HANDBOOK OF PHYSIOLOGY

SECTION 1: Neurophysiology, VOLUME II

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of physiological knowledge and concepts

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Motor mechanisms —introduction: the general principles of motor integration

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SPINAL INTEGRATION

The Spinal Animal

IT IS A COMMONPLACE OBSERVATION in biology that the caudal animal segments are capable of a certain degree of coordinated behavior following transection of the neuraxis. The writhing hind segment of the snake or worm, the decapitated fly going through the movements of grooming its absent head, the headless chicken flying some yards after the axe has fallen, are within general experience. We can therefore proceed directly from the assumption that some part of motor behavior is provided by the spinal mechanism alone to examine its components and organization. At the outset, however, we are immediately impressed by the lessened range of such spinal behavioral activity in vertebrates as compared with invertebrates, and in monkey and man compared with the vertebrates possessing less complex nervous systems. The phylogenetic change that is implied in the term 'progressive encephalization of function' may be more apparent than real, for earlier estimates of the optimum reflex recovery in spinal man have had to be revised in the last 15 years in the light of improved methods of care of the human patient with transected spinal cord (59, 67).

The idea of 'sympathies' between different parts of the body had long preceded the processes of 'reflection' put forward by Descartes in 1662 to categorize such involuntary effects as a blink of the eyes in response to a threat. Opinions regarding the portion of the nervous system responsible for 'reflection' slowly changed from the pineal gland to the limb plexuses, later to the central nervous system in a general pattern. Sherrington (88) pointed out that the fundamental experiment was that of Stephen Hales in 1733 who demonstrated that the responses of the spinal frog are irrevocably lost following destruction of the spinal cord. In 1750 Whytt widened the conception of reflex action and noted the period of suppression of reflexes immediately following decapitation. Grainger in 1837 showed that the gray matter of the spinal cord was essential to reflex function. As Sherrington remarked, the importance of the next step, the Bell-Magendie experiment that defined the sensory and motor nerve roots, can hardly be overestimated.

Through the nineteenth century the unravelling of the pattern of reflex response advanced rapidly. In 1823 Mayo showed that the pupillary reflex to light depended on the integrity of one small segment of brain stem. Legallois in 1826 discovered that injury to one small portion of the medulla paralyzed respiration. Prochaska and Marshall Hall refined the idea of 'reflex function' and greatly stimulated interest in the subject (35, 47). The considerable contributions of biologists and general physiologists, such as Bethe and Loeb, in the following 80 years, should also be mentioned. It was the painstaking observations of Goltz (39) and his associate Freusberg on the chronic spinal dog that established the general pattern of mammalian spinal behavior that was later to be subjected to detailed analysis by Sherrington.

If segments of lumbosacral spinal cord survive, the skeletal musculature, after an initial period of inert flaccidity of variable duration, begins to show reflex responses. In the dog this period of severe 'spinal shock' may last several hours. In monkey and man it lasts from one day to three weeks. The first reflex to recover is usually some contraction of the adductors of the thigh, or dorsiflexors of the ankle in response to a pinch of the foot. In some animals the knee jerk is the first response to be obtained. In man a small flexion movement of the toes in response to stimulation of any part of the sacral segments may be the first to appear (28). Day by day the flexion of hip, knee and ankle becomes more regularly elicitable and requires less intense stimulation. At the same time the area from which this, the flexion reflex, can be elicited spreads from its 'focus' in the outer border of the foot to include the whole plantar surface, then the dorsum of the foot, the anterior aspect and then the whole leg. Finally it may be obtainable from any part below the level of transection, including the abdominal wall if the segmental level is high enough. As the nociceptive flexion reflex thus recovers, the automatic response of the bladder and rectum, at first exhibiting only the weak rhythmical contractions in response to distention resembling those of the animal with exsected spinal cord, abruptly begins to discharge the contents of these organs more forcefully and completely. At this point more effective bladder and rectal contractions can be initiated by stimulation of the perineum and later of the limbs. This more coordinated reaction is reflex urination and defecation.

In the acute decapitate-cat preparation commonly used in classroom experiments, natural stimulation produces little if any response; the tendon reflex is present and stimulation of nerve trunks and roots can elicit flexion reflexes. In the chronic spinal state, as the flexion reflex gains in recovery, its elicitation in one limb is associated with extension of the opposite limb (crossed extension). In the first weeks the hind limbs of the dog are found in a posture of tremulous flexion, apparently the result of multiple minor reflex flexions, though at times a feeble stretch reflex ('the pluck reflex') is observable. The knee jerk is brisk and of large amplitude. Under favorable circumstances, particularly when ulceration of the skin and infection of the bladder have been avoided, and with greater frequency in the spinal dog than in other animals, the limbs may then begin to extend at intervals, the knee jerk becomes clonic, and passive flexion of the limb meets a resistance that increases, then melts as the limb is passively flexed. This is due to recovery of the stretch reflexes of the extensor muscles. Passive flexion of one limb then commonly initiates extension of the other (Phillipson's reflex), followed by an alternating stepping movement. The flexion phase of the step is the proprioceptive flexion reflex. A moving coarse contact from the ball of the foot onto the toes while the limb is flexed may then initiate a sudden powerful extension of both limbs (the extensor thrust) which in full recovery becomes the first phase of a gallop rhythm.

When such a state of reflex recovery in the isolated segments of spinal cord is reached, a number of other reflexes make their appearance, for example the coitus reflex from appropriate stimulation of the perineum, the shake reflex from stimulating broad areas of the skin of the back and thorax, and the scratch reflex from nociceptive, particularly moving, stimuli in any part of a saddle area that covers the shoulders and neck. The focus of the scratch reflex lies behind the ear. The whole field covers the back of the head and neck and a saddle-shaped area over the shoulders. Only the caudal part of this area is demonstrable by spinal transection. The focus behind the pinna can be shown in the decerebrate animal (90). Goltz and Freusberg observed shivering in the muscles supplied by isolated thoracic segments of spinal cord in response to cold applied to the corresponding skin segment, although shivering of the limbs is not obtainable in the chronic spinal preparation (91). For further details of these responses the reader is referred to the original works of Goltz (39) and the writings of Sherrington (87, 92).

Spinal Shock

The nature of spinal shock, the depression that precedes recovery of spinal reflexes in the chronic spinal state, is still obscure. It does not affect reflex mechanisms rostral to the transection. Stimulation of a large pathway such as the pyramidal tract still provokes motor discharge. With facilitation by strychnine the flexor and tendon reflexes can still be obtained in the period of spinal shock. The motor neurons preserve a natural histologic appearance. The process of recovery of reflexes is a progressive lowering of threshold, and spinal shock may therefore be regarded as a raised threshold of spinal reflexes of unknown cause. It is observed at all levels of transection caudal to the midpontine level, above which a transection of the brain stem is followed immediately by the selective heightening of reflexes called decerebrate rigidity. The assumption is therefore made that some mechanism in the tegmentum of the upper pons and brain stem can counteract spinal shock. The shrinkage of motor neuron pools for measured fractions of the flexion reflex during spinal shock suggests withdrawal of a 'subsidy' of spinal excitatory process (16). A lesser depression of reflex function follows isolated section of corticospinal innervation, suggesting that the chief element in spinal shock is the sudden loss of any large facilitatory pathway (62). There is no evidence that any of the events of spinal shock or recovery from it are pharmacologic reactions comparable to the hypersensitivity of cholinergic end organs following loss of their innervation. The induction of parathyroid tetany in the chronic spinal animal (103) after spinal shock is associated with the development of clonic tetanic spasms in the parts headward of the transection a little earlier than those related to isolated segments, but the general excitability is little if at all lowered in the isolated segments.

It has recently been demonstrated (19, 34, 64) that, at the motor nerve ending in muscle, very small quanta of excitatory transmitter substance are continually bombarding the muscle membrane, regardless of the passage of nerve impulses. If such a phenomenon can be shown at central synapses, it would at once explain how the loss of a transmitting pathway of potent effect could result in depression of all other excitation of the motor or internuncial neuron.

Deterioration of Spinal Reflexes

Recovery of extensor reflexes in spinal man proceeds to an optimum condition that is attained only with the most effective nursing care. It is commonly observed that any intercurrent infection, particularly that associated with trophic skin ulceration, results in an enhancement of flexion reflexes with a loss of extension reflexes, including diminution and ultimate loss of knee jerks. The lower limbs then become drawn up in continued flexion (paraplegia-in-flexion). The flexion reflex can then be set off by any stimulus, often in the form of 'spontaneous' flexor spasms by the pressure of gravity on dependent parts. With a strong stimulus it becomes associated with urination and profuse sweating over the areas of skin innervated by the sympathetic outflow from the isolated segments of cord if these include L2 or higher segments. If the midthoracic segments of spinal cord are included, a rise in arterial pressure, often extreme, is associated, owing to vasoconstriction in the splanchnic area. This widespread reflex effect from a single stimulus was termed the 'mass reflex' by Head & Riddoch (48). In contrast to the state of optimum recovery of spinal reflexes, where the response is adapted to the locus and nature of the stimulus, the mass reflex can be viewed as a loss of 'local sign.' It could be related to a breakdown of canalization in the spinal nerve-net of such kind that pharmacological alteration of selective transmission could account for the change. The observation of a comparable phenomenon in untreated combined system disease of the spinal cord in man, where degeneration of the dorsal column extends from the thoracic to the lumbar and sacral segments and leads to loss of spasticity and tendon reflexes with parallel increase in flexion reflexes and ultimately paraplegia-in-flexion, points to another mechanism. In this case the progressive loss of the collateral branches of dorsal column fibers responsible for extensor reflexes leads to reflex disequilibrium and flexor preponderance. It is likely that the emergence of the mass reflex is always a similar disequilibrium. Conversely, ischemic damage to the lumbosacral intermediate grey matter can, by selectively damaging multisynaptic transmission, result in great exaggeration of extensor postural reflexes at the expense of nociceptive flexion, for this is our interpretation of the phenomenon of Häggqvist (46) and van Harreveld & Marmont (101).

Reflex Pattern

Following his early studies in the spinal dog, Sherrington successfully undertook a long series of researches directed to the unravelling of the pattern

of interaction of spinal reflexes (87, 89, 92) and ultimately to the nature of reflex transmission. It was shown that for each type of reflex response a particular or 'adequate' type of stimulus was necessary, and that in circumstances of concurrent multiple stimuli, the nociceptive stimulus was 'prepotent.' Reflexes exhibited the phenomena of facilitation and spatial summation. At some point in the reflex network the effects of different afferents converged on the same motor neuron—the final common path. The discontinuity of afferent, interrelated neurons and motor cells demonstrated by Kölliker, Ramón y Cajal, Golgi and van Gehuchten, with the postulate of 'dynamic polarization' of these histologists was incorporated into the 'synapse' for which Ramón y Cajal demonstrated the 'end feet' on the surface of the nerve cell and its dendrites. Sherrington also proved that spinal inhibition is an active process and demonstrated its reciprocal relation to excitation of the motor neurons of antagonists. Like excitation, inhibition is capable of temporal and spatial summation. Where neurons already discharging in response to activation by one path were blocked from any exciting effect by the previous activation of another path converging on them, the effect was shown to be passive (occlusion) and altogether different from inhibition (16). Of the neurons available to either of such converging afferent pathways, few were excited by weak stimulation of each path; yet the others were still excited subliminally and could be discharged by weak stimulation of both paths together. For each reflex response there was therefore a wide 'subliminal fringe' (29) of affected but unresponsive neurons.

From such principles there emerged a concept of a network of anatomically predetermined connections, the effectiveness of each depending on the number of end feet supplied to each pathway. The muscles, being collections of motor units, are related to columns of motor cells in the spinal gray matter, their functional significance residing in the fixed synaptic relationship supplied to the motor neurons in the course of development. Earlier attempts to prove a plasticity of central connection were disproved by the experiments of Cunningham (18) and others and lately of Sperry (94) who showed that transplantation of nerves or muscles so as to perform antagonistic function in the postnatal mammal could not determine change of reflex effect.

Postural Reflexes

Following the complete flaccidity of spinal shock the posture of the limbs is at first an intermittent flexion. As the flexion reflex becomes more active its after-discharge is at first more prolonged. A pluck of a flexor tendon (e.g. that of the tibialis anterior) may elicit a flexor jerk at this time. The emergence of the reflexes of extension is associated with curtailment of flexor after-discharge and intermittent extension of the limbs. For a time alternating stepping then appears. In full reflex recovery the hind limbs of the spinal dog are sufficiently extended to support the hind quarters, although they have to be propped passively in this position (39, 87). The posture is liable to sudden lapses owing to intermittent brief flexions or to the onset of stepping. Lateral stability is impaired by overactive adduction. These spinal antigravity postural responses are due to the presence of the spinal stretch reflex (27) which can be sustained for long periods and is associated with very brisk tendon reflexes, ankle and patellar clonus. Under certain circumstances the stretch reflex may be demonstrated in flexor muscles, but this response is very inactive in the spinal state.

The stretch reflexes in both spinal and decerebrate preparations are affected to some extent by cutaneous stimulation, although they are in no way dependent upon it. Thus if the animal is caused to sit up on the rump, both lower limbs tend to extend stiffly, more so if the spine is tilted backwards. If the animal is tilted forwards so as to flex the hip joints, the knee and ankle tend to flex. There is little change if the hind quarters are laid on one side, although the lower limb may then tend to flex briefly. Pressure on the pads of the feet increases the extensor resistance and, if the limbs are previously flexed, to elicit an extensor thrust. These effects from cutaneous pressure are evidently spinal fragments of what in the thalamic animal are identified as body-on-body righting reflexes (68, 77) and contactual 'positive supporting reaction' (69). They are particularly well developed in the skin of the feet and lateral thighs as the reflex of 'ipsilateral extension' analyzed by Hagbarth (45). A decapitated insect can right itself by contact reactions (10) and the spinal segments of an eel can right themselves; but the mammalian spinal reflexes preserve a more local character. The relationship of the spinal extensor thrust to the gallop mode of progression, and to the powerful leap reflex of the thalamic animal (68), is the same as that of the stretch reflex to spinal stepping and of both to the more fully developed progression at higher levels of transection of the neuraxis. The spinal mechanism thus provides all the elements of postural responses. It is their integration with the whole of the organism that is lacking.

Stretch Reflex

Part of the fundamental proof of the stretch reflex (63) was the demonstration that the afferent roots pertaining to each muscle were not only necessary for a stretch reflex within that muscle but for the background of postural reactions in general. It is possible, as Ranson & Hinsey (80) showed, to induce some extension of the deafferented forelimbs of the cat by putting the decerebrated animal in the posture for maximal tonic labyrinthine and neck reflex but only after the device of section of the cord below the cervical enlargement. Deafferentation raises the threshold for all other reflexes, phasic as well as postural, and abolishes after-discharge.

The receptor function of the muscle spindle will be discussed in a later section. Here we may note only the regulation of the spindle response by the intensity of small-fiber motor innervation (56, 58) and the uniquely monosynaptic nature of the stretch reflex response (65). The receptor has most excitatory effect in the deep short-fibered postural segments of the same muscle that is stretched. Thus stretch of the gastrocnemius excites chiefly soleus motor neurons; of the vastus, the crureus. Stretch of the quadriceps excites the soleus to some smaller extent but not vice versa (20, 32). The patterns of stretch effects from adductors and abductors, manifestly important in postural stability, have not yet been worked out.

The adjuvant effect of the small-fibered motor innervation allows delicate facilitation of this system to energize powerful stretch reflexes, and it is possible that most motor and certainly postural function is self-energized. Little is yet known of the reflex sources by which the small-fibered motor system is thus facilitated, although cutaneous tactile stimulation of the foot can thus provoke gamma-fiber facilitation (56), and the pontine brain-stem mechanism can influence it powerfully (33, 43).

Two local factors tend to limit the self-energizing effect of the stretch reflex, the slackening of the muscle spindles when the muscle contracts and the high threshold inhibitory effect (autogenetic inhibition) of tension on the tendon organs (42). Each natural stretch reflex response is therefore an equilibrium in which a balance of proprioceptive excitation counters autogenetic inhibition. This equilibrium gives plasticity to the response (20) so that an increase in length of the muscle is followed first by an increase in its contraction, then some lessening of contraction immediately the new length is reached (lengthening reaction). Conversely, any sudden shortening of the muscle is associated with a cessation of discharge in many units followed by recovery of some (shortening reaction).

Coordination of Spinal Reflexes

Even the most simple spinal reflex shows a complexity of organization directed to purposive integration of the various discharging motor units. Nociceptive stimulation of the outer border of the foot induces flexion with some adduction, while stimulation of the inner border yields flexion with some abduction. The corresponding fractionation of the groups of neurons representing each of the corresponding flexor and adductor muscles has been estimated quantitatively (16). The adaptation of response to locus of stimulus is attributed to the inborn pattern of synaptic arrangement of the central terminals of the afferents from each locus. In more elaborate pattern the spinal scratch reflex involves appropriate flexion of the hind limb with adduction, or adduction together with curvature of the spine sufficient to bring the scratching paw within a few millimeters of any stimulated spot in the wide sensory field. In addition this reflex secures a tonic, continued postural contraction in some muscles as well as a rhythmic flexion-extension of those that determine the scratching movement. Likewise reflex urination and defecation when fully developed are associated with appropriate posturing of the hind limbs and tail and even the terminal scratch of both feet. It is therefore certain that the spinal motor mechanism not only presents a predetermined reciprocal relationship of antagonists but also all the requisite combination of prime movers, synergists and fixation muscles appropriate for the performance of spinal reflex behavior. If stimuli with conflicting effects are delivered concurrently, the spinal mechanism either resolves the response in favor of one at the expense of the other or exhibits a rhythmic alternation of response.

Sherrington's studies of the scratch reflex (89, 93) included the demonstration by degeneration experiments that the reflex pathway from the cervical and thoracic roots to the lumbosacral segments traversed the lateral tracts lying close to the gray matter in the spinal cord (propriospinal tracts). For the integrated spinal response of alternate stepping of the limbs the presence of the grey matter of segments lying immediately rostral to the cell columns of the chief flexors and extensors in the lumbar and cervical enlargement appears necessary. In these regions the studies of Ramón y Cajal (79) indicated that the interneurons that govern such coordinated spinal responses are in

the intermediate nucleus in the most medial part of the base of the anterior horn, their axons being directed to the chief flexor and extensor cell columns, both ipsilateral and contralateral via the anterior commissure, and to the propriospinal tracts. Certain 'funicular' cells along the outer margin of the anterior horn probably serve a similar function (17, 79, 95) and show marked chromatolysis following section of dorsal roots (102). In the high cervical region these poorly defined groups of cells appear to be devoted to the coordination of neck reflexes and a lateral group in the dorsal horn (n. cervicalis lateralis) projects to the lateral part of the tegmentum of the midbrain and to the cortex (72). It is possible that the severe depression of ipsilateral reflexes in the cat and monkey after high cervical hemisection results from asymmetry of this coordination. In the medulla the corresponding anatomical structure is the reticular formation the integrity of which allows even more general integration of reflex behavior. Indeed, as a result of his studies of the development of reflex behavior in the amphibian embryo, Coghill (15) concluded that an integrated progression movement mediated by the brain-stem reticulum was the primary response of the developing nervous system. The spinal reflexes in his view were fractions of this coordinated behavioral unit and were more slowly evolved.

SUPRASEGMENTAL INTEGRATION

Tonic Neck and Labyrinthine Reflexes and Decerebrate Rigidity

If transection of the neuraxis is made above the second cervical nerve roots, flexion, extension and rotation of the neck and occipitoatlantal joints lead to modifications of the posture of the limbs. Such changes are minimal in degree with sections behind the midpontine level. With a background of decerebrate rigidity following transection above the pons, the tonic neck reflexes become regularly demonstrable (68, 77) as well as postural adjustments related to position of the labyrinths (tonic labyrinthine reflexes). The facilitory effect that underlies decerebrate rigidity must in part be related to innervation of spinal segments reaching the spinal cord by the vestibulospinal tracts, for section of these lessens its intensity (60). The greater part of the facilitation of all spinal reflexes that is associated with decerebrate rigidity appears, however, to be related to the activity of the pontine reticular formation. The general area concerned is the excitatory reticular formation of Magoun and his associates (83, 86) with an efferent pathway in the reticulospinal tracts.

Decerebrate rigidity is lessened on the side of an eighth nerve section and intensified on the opposite side. It is little affected by bilateral section of the eighth nerves. It is increased in one limb by deafferentation of the opposite limb, increased in both forelimbs by postbrachial section of the spinal cord (Schiff-Sherrington phenomenon) (84) and in the hind limbs by deafferenting the forelimbs (13). These findings indicate an equilibrium of effects, the proprioceptors of each limb facilitating its own stretch reflex and tending to inhibit those of other parts, each labyrinth tending to facilitate ipsilateral extensors and restrain contralateral. In addition each fastigial nucleus of the cerebellum, through the hook bundle of Russell to the reticular system, was found by Moruzzi & Pompeiano (73) to influence profoundly the distribution of rigidity. A lesion of the caudal pole of one fastigial nucleus can abolish rigidity on the opposite side and enhance that on the same side, yet destruction of both fastigial nuclei leaves the rigidity unaffected. The effect of a unilateral fastigial lesion is based on inhibitory effects arising from the proprioceptors of the ipsilateral muscles. Decerebrate rigidity from intercollicular section is therefore a disequilibrium of a complex postural integration of proprioceptive facilitory and suppressor effects, arising in the muscles of the limbs and reflected back as a predominant extensor posture in which the tonic neck and labyrinthine reflexes determine the major pattern. The most fundamental single element in this complex appears to us to be the enhancement and integration of the proprioceptive positive supporting reaction by the pontine reticular formation. This is associated with increased discharge of the small-fibered gamma motor system (33, 43). The contactual type of positive supporting reaction that is grouped with the proprioceptive together as the 'Stützreaktion' by Rademaker (78) is notably absent.

In decerebrate rigidity there is also an exaltation of some flexion reflexes (20, 44) and of sympathetic and parasympathetic (bladder) responses indicating that an incongruous mixture of related and unrelated reflex effects is released. We would doubt the existence of a pontine center (97) for urination, for example. There is no good evidence that the pontine reticulum is organized as a center in terms of a series of specific categorical functions, although in ascending levels the first stage of simple grouping and facilitation of excitatory (and to a less degree for

inhibitory) effects for total bodily responses of both somatic and autonomic kinds can be recognized.

Righting Reflexes and the Midbrain Animal

Although the decerebrate animal exhibits the tonic neck and labyrinthine reflexes and may be able to stand for a time if appropriately propped upright on its limbs, the attitude is a caricature of that of the normal animal. There is no response to correct some inequality of posture, and once thrown off balance the animal topples over in a passive manner with complete absence of righting. The reactions are greatly different if the level of section is cephalad to the midcollicular level where sequential reactions begin to make their appearance. The difference is most apparent in the thalamic or decorticate preparation (6, 68). Whereas the decerebrate and spinal mammalian animals exhibit static reactions, the thalamic one shows integrated kinetic behavior. It can right itself, raise itself to standing position, adjust its posture to surface and gravity, and exhibit progression. Magnus & de Kleyn (68) first analyzed the body-on-body, neck-on-neck, neck-on-head and labyrinthine components of the righting reflexes. Their anatomical mechanism is still in some dispute. The simple structure of the red nucleus in the higher mammals, and the correspondingly small size of the rubrospinal tract, make it unlikely that this structure alone is responsible for the remarkable variety of activity that Rademaker (77) claimed depended on its integrity. Lorente de Nó (66) found that section of the most cephalic part of the raphe of the pontine reticulum could release decerebrate rigidity. Carpenter (14) has accurately destroyed the red nucleus bilaterally in the monkey with no result other than hypokinesia. The scattered reticular system of the midbrain and its complexity of interlacing fibers is less easily identified by physiological experiment and is more likely to serve the critical adaptation of function whose removal results in decerebrate rigidity. The complex fiber system that enters the capsule of the red nucleus and the interlacing network of the field of Forel that lies immediately cephalad constitute a main traffic intersection in the extrapyramidal motor system of the higher mammals.

The dorsal part of the midbrain tegmentum where the dorsal mesencephalic nucleus lies medial to the oculomotor nuclei is the most cephalic part of the system for coordination of the eyes with head posture (51, 77). The main portion of this complex extends down as far as the upper pontine reticular areas and there relates head and eye movement to the rest of the body. It interrelates the vestibular, mesencephalic fifth and various oculomotor nuclei. Damage to any part of it, but particularly at the pontine level, results in tonic deviation of the head and eyes to the same side. It appears to be responsible for body-on-head righting reflexes and compensatory movements of the eyes with movement of the head. The more intense rigidity, without release of the small-fibered gamma motor system, produced by the anemic method of decerebration (33, 43), with persisting effects of cerebellar stimulation still present, indicates that, with slightly more cephalic parts of the ventral mesencephalic reticular nuclei intact, an additional adjuvant factor acting directly on extensor motor neurons is added to the intercollicular type of rigidity. With transection just above the superior colliculus this more intense but more variable type of rigidity is often seen. It tends either to alternate with running or clawing movements of the forelimbs, or intense flexion of the forelimbs (54, 55, 76). The superior collicular level is evidently critical in the sense that small anatomical differences in section result in profound changes in posture (55). The conclusions of Magnus (68) and Rademaker (77) that the righting reflexes are present in the midbrain animal and absent after intercollicular section are misleading. Elements of the kinetic righting reactions begin to appear in the ventral mesencephalic tegmentum but chiefly in terms of very tonic and disequilibrated body-on-body and head-on-body responses. This indicates that modulation of proprioceptive responses by the effects of cutaneous and subcutaneous pressure must begin to become effective at this level. The descending pathway must be independent of that of decerebrate rigidity, for section of the vestibulospinal tract releases contact supporting reactions when these can still be abolished by intercollicular section (61).

It is characteristic of the reactions of the midbrain animal that they represent in high degree the tendency to swing violently to the opposite response, a feature that is seen in spinal reflexes as 'successive induction' (89) and 'rebound' (92), and interested Sherrington as one of the factors that determined the turning point in spinal stepping. Rebound is peculiar to types of reflex (e.g. ipsilateral extension) where a conflict of central effects is combined with a type of response that tends to lessen the natural stimulus (negative feed back). This in the spinal animal leads to galloping movements following an

extensor thrust and to rhythm in the scratch reflex. In the thalamic animal it leads to clawing, jumping and running movements, and in righting enables the under limb, by alternate flexion and extension with increasing abduction, to push the body from the lateral to the upright position. It is this tendency to alternation that gives the thalamic preparation its kinetic, dynamic behavioral aspect, compared with the static fixity of response of the decerebrate animal. Only with an intact subthalamic region does more regular and progressive righting of the body appear and then only after an interval of time after section. Thus the 'midbrain animal' is an inconstant anomaly exhibiting transitional states. In man, however, classical decerebrate rigidity is rarely compatible with survival, and as a result of disorder at midbrain level a static posture of rigidity in flexion of the upper limbs with extension of the lower limbs ('decorticate rigidity') is frequent.

The elements of postural adaptation are all present as spinal reflexes. Their development of energy adequate to overcome gravity actively and of sequences capable of effective performance requires the presence of the pontine and midbrain reticulum and cerebellum.

Cerebellar Function

The early physiologists thought that the cerebellum coordinated labyrinthine with other postural reflexes, for the symptoms of cerebellar disease so closely resemble those of vestibular disorder. The demonstration that the labyrinthine and neck-righting reflexes remained intact after decerebellation appeared to deny this hypothesis. Yet the ingenious analysis of Rademaker (78) demonstrated that it is the overactivity of some righting reactions, particularly of those involving lateral displacement of the limbs in space, and of the positive supporting reaction which give cerebellar ataxia its most characteristic features. The modulation of these kinetic responses that make them appropriate in relation to correction of total bodily posture is lacking. The means by which the cerebellum performs such adjustments still eludes us. It is probably significant that the body-on-body righting reflex is abolished by decerebellation, while the effect of posture of one limb on that of the others (a true spinal reflex effect) is greatly increased. In some way the cerebellum must interrelate these two (together with visual and labyrinthine effects). The intense asymmetry in the postural effects of one limb on the others produced by unilateral lesions of the fastigial nuclei by Sprague & Chambers (96) and by Moruzzi & Pompeiano (73) indicate an amplifying system for proprioceptive righting reflexes, in both positive and negative senses. The response has its origin in the vermis and reaches the pons via the inferior peduncle (74). The remaining neocerebellum and its outflow via the superior peduncle would appear to be the likely mechanism for modulation of contactual types of positive supporting reactions and body-on-body righting. If, as we have seen, coordination by combination of effects is in its essential elements a function of spinal reflexes, the contribution of the cerebellum appears to be in the general area of adjustments of posture by environmental factors. Its effects are most obvious on proximal limb muscles.

Hypothalamus

In addition to its control of endocrine function through the pituitary gland, its regulation of water balance and temperature, the hypothalamus is important in the integration of emotional effects, both vegetative and motor. Graham Brown & Sherrington (41) showed that stimulation of a sharply localized point on the cut surface of the midbrain of the decerebrate cat could regularly elicit the reflex mimesis of anger, including side-to-side lashing of the tail, protrusion of the claws, a pilomotor reaction and a great rise of arterial pressure. The same response can be elicited by certain acoustic stimuli in the decerebrate cat (36). Graham Brown has elicited a respiratory rhythm closely resembling laughing from a nearby point in the midbrain of the chimpanzee (40). These points both are closely related to that from which pupillary changes, vasomotor and visceromotor phenomena can be obtained, and correspond approximately with the descending hypothalamic pathway of Magoun (70) which evidently has relays in the brain-stem reticular formation (12). The coordination of these different effects into a characteristic behavioral display must therefore be related to patterns of connections in the reticular formation of the brain stem and spinal cord. The total reactions of anger and pleasure are uncommon in the decerebrate cat, even when kept in the chronic state (7). Bard (1, 3, 6) showed that the integrity of the hypothalamus was the essential factor which accounted for the facility of pseudaffective reactions of decorticate animals. The reactions ('sham rage') are unusually violent in proportion to the stimulus,

an indication that the function is released, presumably from cortical control.

The part played by the hypothalamus in the determination of motor behavior is difficult to assess. From various anatomical points in the posterior hypothalamus poorly restricted effects on pupils, heart, arterial pressure, gastric and intestinal motility, with various motor responses, can be obtained by stimulation; this field has been reviewed by Ranson & Magoun (81), by Beattie (8) and others, and by Hess (49, 50). It remains to be shown what particular elaboration of any one of these transmitted effects is served by their hypothalamic connections. The outstanding functional significance of the region would appear to be the general integration of these various effects into the patterns of sleep and wakefulness, apathy and attention, pleasure and fear. The more appropriate regulation of emotion and visceral activity in relation to the environment requires the functional activity of specific areas of the cerebral cortex. The extent to which these general hypothalamic motor functions are also subject to endocrine control is not yet clear.

Thalamic (Decorticate) Animal

Of the many reactions possessed by the thalamic or decorticate animal that are absent in the decerebrate, we have already seen how the righting reflexes have been attributed to the activity of the midbrain, and emotional and visceral responses to the hypothalamus. It is questionable whether the thalamus per se adds further to motor behavior, other than by its reciprocal relationship to the cortex. The subthalamus, including the subthalamic nucleus and the upward extensions of the red nucleus and substantia nigra, and the important fiber tracts interrelating these with the basal ganglia and brain-stem reticular formation, are important for the elaboration of righting reflexes and of progression (54, 55, 82). In higher mammals it is not yet certain which of these structures makes possible the intensification of kinetic activity that distinguishes the thalamic animal from the decerebrate. All that can be concluded on present information is that whereas the posterior hypothalamus contributes behavioral drive, the subthalamus endows more perfect integration of motor response.

The thalamic and decorticate cat (6) and dog (78) present a nearly natural distribution of posture. It is notable that when the limbs are suspended in space an extension posture appears which disappears immediately the limb makes contact with the ground (6). The tactile placing reactions are absent, and a limb hanging over the edge of a table remains extended. Yet by asymmetry of broad contact with body surface the animal can right itself, and with marked displacement a limb posture will be corrected. The extended posture has elements of spasticity and is contralateral to a unilateral decortication. The decorticate monkey also shows spasticity which is strongly influenced by asymmetrical body contact, being an extension of the under limbs when the animal is lying on one side. The uppermost arm and foot are then more flexed, and traction upon them elicits stronger flexion (the traction reaction). When the animal is sitting, the arms are flexed, the lower limbs extended, and the traction reaction is present in both upper limbs. If he is leaned forward in sitting posture, the arms extend; if leaned back, they flex more; if supported on hands and feet, all limbs show a positive supporting reaction. The kinetic body-on-body righting reflexes, as well as the labyrinthine righting reflexes, make gradual recovery from decortication and are the basis for the somewhat stiff and awkward automatic behavior of the chronic 'thalamic' animal. All the elements of these responses can be demonstrated in man following some types of capsular hemiplegia (100) but are limited tonic types of reaction without kinetic effectiveness.

The intense spasticity of many cases of capsular hemiplegia in man presents motor effects that cannot be directly compared with the motor status of the thalamic or decorticate animal. The hand may be tightly clasped in a fist, trapping the thumb under the other fingers, or the wrist may be flexed but strongly pronated with extended fingers. An intermediate type presents extension of the wrist with overextended metacarpophalangeal joints and strongly flexed (clawed) interphalangeal joints. In all these different postures the traction reaction is intensely overactive, and in the last variety clonus of the finger flexors is prominent. The two extremes of postures of the hand can occur without spasticity or increased tendon reflexes in the conditions of dystonia and athetosis. When they appear in combination with spasticity as a result of capsular lesions, a more general rigidity of all muscles in the corresponding limbs is also present. It is therefore assumed that such intense spastic states are a combination of released spastic traction reaction of the type produced by cortical lesions with a superimposed facilitation of either avoiding or grasping extrapyramidal mechanism of the type that is called dystonia.

We shall discuss these effects separately below (Extrapyramidal Motor Responses). More complete transverse lesion at or just above thalamic level in man is seen in cases of severe cortical damage from anoxia, cortical and subcortical degenerative diseases such as destructive types of encephalitis or diffuse sclerosis. In such conditions, or following unilateral hemispherectomy, the motor status more closely resembles that of the thalamic animal.

Control of Movement by Cortex (Rolandic Area)

In the whole of the above discussion the part played by the pyramidal tract in movement has been set aside. Its function is obviously related to the cerebral cortex. Its increasing development in the higher mammals and the corresponding greater severity of symptoms resulting from lesions of it point to increasing importance of a particular aspect of motor function, particularly in relation to prehension in the primates. In subsequent chapters the patterns of anatomical representation in the cerebral cortex and their relation to behavior will be discussed fully. Here we shall attempt to outline only the functional capacity of cortical mechanisms for movement in relation to the subcortical integration that has been discussed above.

The most obvious immediate change resulting from complete ablation of the precentral gyrus of one side in the monkey is a flaccid paralysis of the lower part of the face and of both limbs on the opposite side. From the beginning it is seen that the weakness of lip muscles is only partial and is greater for some movements than others. Within a few hours the animal begins to use proximal muscles of the lower limb. Within 2 or 3 days the affected arm begins to be used in climbing, particularly if the animal is frightened, and the hand and foot may be hooked onto cage wire in clumsy fashion (25). At this time the tendon reflexes are becoming more ample and brisker than those of the other side. After 1 to 2 weeks, when the animal is laid on the operated side and the fingers or toes of the uppermost side hooked over the examiner's finger and thus pulled upwards, a counter-contraction of the flexors of the limb may be felt in response. If, while so suspended, the animal is suddenly lowered in space, the fingers (or toes) will be felt to contract as well as the other flexors of the limbs. This is the reaction that is called by us the 'traction response' (22, 30), and by Fulton and his associates (11, 37) the 'grasp reflex.' We prefer to reserve the term 'grasp reflex' for a type of reaction triggered by a contactual stimulus (85).

A few days before the appearance of the 'traction response,' passive stretch of a flexor muscle of the upper limb or an extensor muscle of the lower limb begins to encounter some resistance. At first this is in the proximal muscles and is felt only towards the end of a stretch. This is the beginning of spasticity and is associated with increasing briskness of tendon reflexes in the same muscle (21). In the course of time the phenomena of 'clasp-knife' melting of spasticity during stretch and clonus of tendon reflexes may appear, but these are a matter of degree of spasticity and are more apparent with capsular lesions. It will be noted that whereas spasticity is a response limited to the muscle that is stretched, the traction reaction is a response in all the flexors of the limb (already tense) in response to increasing stretch of any one of them. The traction response when well developed can be elicited in all the flexor muscles if all of the afferent roots to the limb but one are sectioned. It is felt in the fingers and wrist when only the shoulder flexors have afferent innervation, or vice versa. It cannot be elicited from a deafferented muscle. The traction reaction is affected more obviously than the tendon reflexes by neck and labyrinthine posture.

In the lower limb the appearance of the traction reaction is associated with the appearance of the proprioceptive positive supporting reaction, a pillar-like stiffening or tendency to stiffen of the extensors of the limb when the ankle and toes are passively dorsiflexed. In the lower limb this reaction soon becomes even more evident than the traction reaction, whereas in the upper limb its development is delayed. The pattern of hemiplegic spasticity in the flexors of the upper limb and the extensors of the lower limb is related to the relative preponderance of these two reactions.

Within 2 to 3 days of the appearance of the traction reaction, it is apparent that with sufficiently strong motivation, for example food within reaching distance while the other limbs are restrained or teasing with some unpleasant object under the same circumstances, the animal will make a plucking movement of the limb to bring the object to his mouth. When the reaction can be facilitated by turning the neck, the animal soon learns to turn the neck in addition to plucking at the objects. The triple flexion response remains the same, all joints having to be flexed in order to flex one. The traction reaction is greatly facilitated by laying the animal on the sound side and

is greatly lessened or absent when the normal limbs are uppermost. It is thus 'conditioned' by body contact stimulation.

The 'true grasp reflex,' comparable to that seen frequently in man, is a more complex response (21, 85) than the traction reaction. The fingers are not spastic in the sense of reaction to passive stretch without additional contact (i.e. being pulled upon by tapes) yet counteract a passive stretch on the flexor tendons if this is immediately preceded by a distally moving contact stimulus in a specific area of the palm of the hand or foot (85). The true grasp reflex does not appear for several weeks after removal of one precentral gyrus in the monkey and then only in response to a very firm moving contact. It is unaffected by posture. Its presence is soon associated with some measure of ability to flex the wrist or fingers independently of the proximal joints without actual contact with the hand, if motivation is intense. After some months the hand may close in response to simple coarse contact but does not make any orienting response to the stimulus. In the course of time the thumb may be approximated to the other fingers in this way but never to the degree possible with intact precentral gyrus. With the appearance of a true grasp reflex, spasticity, especially in the flexors of fingers and toes, lessens considerably. All this sequence of events has been observed and recorded in human hemiplegia in our clinic by Twitchell (100).

After bilateral removal of the precentral gyrus [or indeed, of the whole pre- and postcentral area showing antidromic spikes from stimulation of the pyramid charted by Woolsey & Chang (105)], the same sequence of events occurs, although a coarse true grasp reflex may then be obtained within a week of the bilateral operation (24, 26). The animal remains very stiff in movement but can regain an astonishing degree of control of purposive movement by vision.

The type of movement that is completely and permanently abolished by ablation of the precentral gyrus is that we have called the 'instinctive tactile grasping reaction' (21, 24, 26, 85) which is an orientation of the hand or foot in space such as to bring a light contact stimulus into the palm (or sole) when very facile grasping then ensues. The instinctive grasp reaction is essentially an exploratory palpation directed vertically into space from the point of contact. It is a stereotactic contactual response, whereas the grasp reflex is a passive contactual reflex which can become stereotactically directed only by means of vision (26). The foci for the instinctive grasp reaction are the tips of the fingers and their lateral borders, the lips, and the lateral borders of the foot and ankle. Ablation of the hand area of the precentral gyrus abolishes the instinctive grasp reaction in the hand, results in some finger and wrist flexor spasticity, but does not release the traction reaction. Ablation of the oral edge of area 4 releases the traction reaction and proximal spasticity but leaves the instinctive grasping intact (although limited in spatial extent). Woolsey *et al.* (106) have shown in the macaque the corresponding representation of proximal muscles anteriorly and of distal extremities next to the central sulcus. These differences, we believe, are the explanation of the old controversy regarding special function of 'area 6' or '4S' in relation to spasticity and of area 4 to paresis (38, 52, 53), for the criteria then used to judge spasticity identified it only in proximal muscles and hence with anterior lesions.

Following section of the pyramid in the monkey we have noted the same severe loss of use of the opposite limbs as was described by Tower (98) with long delay in recovery of movement which is at first chiefly limited to triple flexion. In our own monkeys some slight spastic reaction returned in terms of a soft reaction to passive stretch, with ample but slow tendon reflexes, and was quite obvious with a partial pyramid lesion. There was slight sustained flexion of the upper limb and extension of the lower; but the traction reaction was not as well developed as after an area 4 lesion, and the animal's ability to convert it to his own ends correspondingly less. A grasp reflex was absent for a long period, then obtained only with heavy moving contact. The difference between precentral and pyramid lesions is therefore chiefly in terms of failure of release of the traction and positive supporting reactions with pyramid lesions, probably owing to integrity of the corticobulbar fibers. As a result of both types of lesion the motor response to a purely visual stimulus, e.g. reaching out for food or support, becomes a simple 'pawing' flexion and extension of the limbs (an adaptation of progression) and is very obvious in behavior when these lesions are bilateral in the monkey (26).

In general terms the exploratory pattern of the tactile placing reaction is comparable to the instinctive grasp reaction, although it is possible to dissociate the two at the cortical level by types of mid-parietal lesions that interfere with the spatial data that are more particularly required for placing (24, 26). In regard to both these reactions the pre- and postcentral cortex and the corresponding lateral thalamic nuclei appear to be inseparable. The pat-

tern of disturbance we have described results from interference with any of these structures, although release of segmental stretch reflexes in the relevant muscles requires damage to the precentral gyrus or pyramidal tract. Similarly the coarse reaction called proprioceptive placing (2, 4, 104) is directly comparable to the 'true grasp reflex' and emerges as a subcortical coordination that eventually becomes very facile in long term survival after removal of the pre- and postcentral gyri (26). It is possible that a large area of moving contact is the adequate stimulus, rather than displacement (proprioception).

Extrapyramidal Motor Responses

Instinctive tactile grasping and placing reactions are released by mesial frontal lesions. We (22, 24, 26) have found that whereas the natural reaction to a light tactile stimulus is a delicate balance between a slight movement of withdrawal or a tentative palpating movement, a lesion of any part of the cingulate cortex, supplementary motor area of Woolsey or area 8 of Brodmann, disturbs this balance in favor of exaggeration of grasping. A lesion including all this strip is necessary to produce the most prolonged release of grasping and placing. This release is associated with disappearance of the contrary withdrawal or 'tactile avoiding reaction.' Ablation of the parietal cortex or of the pre- and postcentral cortex results in release of such avoiding reactions. The cortical pattern of such withdrawal responses appears to correspond to that of the extrapyramidal 'inhibitory' effects found by Tower (99) by cortical stimulation of limbic and related cortex after bilateral pyramid section. A detailed consideration of the cortical mechanisms of tactile and visual avoiding has been presented elsewhere (24, 26). It is necessary here only to point out that this other type of cortical control of movement (withdrawal) is balanced against the instinctive exploratory reactions, so that damage to either results in enhancement of the other. We term this effect 'transcortical release' (22, 23). The tactile avoiding responses are independent of the pyramidal system and are thus true extrapyramidal motor effects. They may be extremely delicate and adroit in the complete absence of both parietal lobes, intermittent contact with only a few hairs then sufficing to elicit elaborate avoiding of a pursuing stimulus. When the 'set' of cortical reactions is altered in this way, it is as if the unpleasant attributes of every stimulus are emphasized at the expense of pleasant or interesting features. The reactions to pain are correspondingly increased in extent and duration. Similarly independent extrapyramidal visual avoiding reactions, also independent of the Rolandic-pyramidal system, can be identified in the monkey deprived of the pre- and postcentral cortex (23, 26) and occasionally in man (24).

The cortical areas active in grasping and avoiding responses are represented in the ventrolateral and anterior thalamic nuclei, respectively. Those concerned with vision are in the lateral and medial pulvinar (26). Direct lesions of these structures at thalamic level, or their severe degeneration as a result of very extensive ablation of the corresponding cortical areas, results in the more intense persistence of the attitudes of grasping or avoiding that are called dystonia. Dystonia is essentially an abnormal persistent attitude such that any attempt of the examiner to displace the limb to another attitude meets increasing resistance. The response to stimulus is altered as in cortical types of grasping or avoiding, but the attitude is maintained for long periods without further stimulus (24).

It will be noted that whereas the spinal reflexes present elaborate organization of the defense (flexion) reflex and at times fleeting glimpses of proprioceptive responses in the flexors, the known postural reactions of the brain stem and cerebellum make little use of flexor responses. Inhibition of extensor responses is more widely found in the reticular formation, for example, where the presumed positive aspect of behavior has not yet been determined. More highly organized withdrawal behavior appears at the highest level as the avoiding responses of the cortex, there related to the phylogenetically more primitive cortical areas. The response to pain, for example, has thus a diffuse cortical representation of this type and, in association with it, negativistic reactions, such as mutism and other akinetic states the physiological mechanism of which is poorly understood.

The function of the basal ganglia has not been mentioned for the simple reason that it is defined only in terms of symptoms and not of positive reactions. The symptoms are in terms of conflicts between the various reactions that we have discussed above. Tonic grasping reactions with long after-discharge compete with tonic avoiding reactions in the condition we recognize as athetosis (21, 26), resulting from lesions of the lenticular nucleus in man. A profusion of cortical automatisms, exploratory and avoiding, often incompatible and therefore leading to grotesque movement, is characteristic of Huntington's chorea, due to degeneration of the caudate nucleus.

More intense rivalry of the same reactions, with rhythmic alternating rebound, results in the parkinsonian type of tremor (21), following lesions at the subthalamic level. The only conclusion in terms of positive function of these structures appears to be that they normally interrelate at their various levels the several conflicting types of cortical and subthalamic mechanisms of movement so as to give priority to one or another type of behavior and thus integrate the total reaction of the organism to the environment. The inhibition relayed from the cortex to the caudate nucleus to the thalamus and back to the cortex reported by McCulloch (31) and Mettler *et al.* (71) appears important in regulating various cortical effects. The poverty of active response to electrical stimulation of the basal ganglia is consistent with such a mechanism. If our view is correct, the mechanism of natural activation and function of these structures will require a complex background of activity for its demonstration.

CONCLUSIONS

We have attempted to describe the general mechanisms of motor behavior in simple terms. Two important general principles emerge. First, every motor reaction has an adequate stimulus, immediate or remote; and second, all that is known of motor function indicates that the nervous system as a whole contributes to each motor act. It is not possible to indicate separate mechanisms for posture and movement. Postural reactions are fundamental in neural organization, and movement in its most elementary form is seen as modifications of postural responses. There is a similar difficulty in defining 'function' which can be used only in a general sense equivalent to activity. The operative physiological term is 'performance' which from spinal to cortical levels can be traced in various grades of refinement and in more appropriate relation to the whole organism and finally the whole environment. A segmental reflex may be perfectly performed in terms of the segmental structures it serves, but for its integration into behavior we have to examine higher and higher levels of neural activity.

In the organization of integration, several arbitrary levels of performance can be discerned. At the segmental level an anatomically fixed synaptic cooperation of agonists and antagonists is preserved. At the pontine level the neck and labyrinthine receptors, through their related portions of the internuncial reticulum, secure a domination, chiefly in terms of additive wider postural reactions, of the segmental reflex pattern. At the midbrain and subthalamic level this in turn is modified by tactile and contactual responses from the body surface, the effect of which has been conspicuously absent or fragmentary in the spinal or decerebrate preparation. The cerebellum contributes importantly at this level. Autonomic mechanisms, like somatic ones, are also seen in fragmentary form at the segmental level and in more complex combinations in the brain stem. The hypothalamus adds the homeostasis of the *milieu interne* and with it the elementary drive that results in total response in coarsest form. With an intact hypothalamus the decorticate animal also exhibits coarse withdrawal or avoiding behavior with appropriate fear reaction and rapid swing to aggression. With such expression are associated total coordinations of autonomic response, already grouped by lower brain-stem mechanisms.

It is the cerebral cortex, with its projections of the exteroceptors, that dominates the whole, able to select items of behavior and modify them in terms of projected reactions. There are only very slender clues as to the mechanism of cortical domination. Our own studies of the defect in movement of the hand as a result of progressing frontal lobe lesions, and the reverse process in recovery (21), convinces us that contactual sensation has an essential part in the full integration of movement in the higher mammals. Though desensitization of one part has little effect on its use, deafferentation of a whole limb in the monkey (75) results in paralysis closely resembling the effect of cortical ablation. Free exploratory movement in space cannot be performed without the ability to make contactual palpatory exploration. This in turn is based on the grasp reflex which is a 'triggered' response. The appropriate contactual stimulus releases an otherwise latent proprioceptive reaction. With loss of the triggering mechanism, the proprioceptive response is continuously overactive to every stretch (spasticity). In this sense the proprioceptive system is restrained by the subthalamic system and harnessed to a series of specific contactual triggers or signals in the pattern of the body-on-body righting reflexes. Both the subthalamic mechanism and segmental reflex are restrained by the Rolandic cortex where the specific activation is further differentiated into the delicate contactual patterns of the instinctive tactile grasp reaction and the instinctive placing reaction. From this point of view 'release' is dedifferentiation or loss of restriction to specific attributes

of adequate stimulus. Suppression with selective facilitation appears to us to be a general principle of neural organization, exemplified not only in the mechanism of prehension but also in the organization of spinal reflexes (extensor thrust), labyrinthine reactions, autonomic function (e.g. urination), learned behavior and Pavlovian conditioning.

Although the precentral cortex offers a mosaic anatomical arrangement of units with direct access to small groups of spinal motor neurons, it is unlikely that any single category of movement requires restricted Betz cell activity. The survival of a small precentral area containing few Betz cells, (for example, 39 counted in one experiment) after removal of all the remainder on one side, was found by us (25) to potentiate a remarkable degree of recovery of exploratory behavior in the opposite limbs. This would indicate a wide extent of facilitating effect on subcortical mechanisms.

In the loss of the placing reactions the corresponding release of neck reflexes indicates that at the cortical level these also are incorporated into fully integrated movement. The exaggerated labyrinthine reactions we have found to follow bilateral ablation of the posterior parietal cortex, a lesion that abolishes the optic righting reflex (26), indicates that in the parietooccipital segment of the extrapyramidal system visual responses restrict and limit vestibular reactions in the same manner we have outlined for the pyramidal contactual mechanism. The release of 'sham rage' by a lesion of the limbic system indicates that differential modulation of hypothalamic mechanisms has its origin in this area. Since the limbic cortex also determines withdrawal and flight behavior (26), it is not surprising that autonomic responses associated with these reactions should also be modulated from this area; but we suggest that they are a by-product of motor behavior rather than an expression of an isolated affective 'center.' Their counterpart, conditioned pleasurable reactions and their associated hypothalamic autonomic effects, is to be expected from the neocortex, as Bard & Mountcastle (5) have hinted, for the context of this area is largely tactile. Sexual behavior, being largely tactile and visual exploratory in nature as well as olfactory, is a prominent association with overactivity of the Rolandic mechanism for exploratory movement. The release of these in the Klüver-Bucy bilateral temporal lobe ablation can also be interpreted as 'transcortical release' from temporal avoiding reactions (26).

The general principle that removal of the 'control of higher centers' results in exaltation of lower 'centers' was recognized by Claude Bernard (9) and others and was further developed by Hughlings Jackson (57). We would prefer to restate the proposition by saying that removal of one of the competing factors in the control of movement at any level results in overaction of the others, and at different levels loss of differentiation of reaction results in lowered threshold for the coarser stimulus.

This introduction to the problems of motor mechanisms does not attempt to correlate the large mass of information on detailed interaction of nuclei and fiber tracts that is available, or the known specific properties of the many neuron systems. Rather it attempts an outline of the general nature of the behavioral problem to which all types of neuronal interaction must ultimately have reference.

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Sensorimotor cortical activities

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CHAPTER CONTENTS

KNOWLEDGE OF THE PARTICIPATION of the cerebral cortex in sensory and motor activities has been gleaned from both clinical and experimental observations. Shortly after the demonstration by Broca of a center for speech in the cortex of the third frontal convolution of the left hemisphere (61), Hughlings Jackson proposed a functional localization and representation of movement in the cerebral cortex (217). His suggestion proved true with the publication of the work of Fritsch & Hitzig (158). These pioneers demonstrated the excitability of the cerebral cortex by means of electrical stimuli and showed by this method that movements could be evoked from certain areas of the cerebral cortex but not from others.

Confirmation of these findings by numerous investigators (18, 40, 70, 143, 144, 153, 154, 211, 281–283, 339) soon extended the knowledge of cortical involvement in sensorimotor activities (see 394, 448 for early references). Before considering this problem in detail, some of the difficulties encountered in the interpretation of data related to the subject should be fully understood.

Difficulties inherent in the use of anesthetics have been largely overcome but others, and particularly those related to the use of artificial stimulation, are still of major importance. It is obvious, as has been frequently remarked, that excitation elicited by means of electric pulses may induce activities which are not

necessarily normal concomitants. Moreover, certain cortical influences participate in a temporal and spatial pattern which is not reproducible with electrical stimulation.

For these reasons, it soon became apparent that substitution of ablation for electrical stimulation might overcome certain of the difficulties (see 320, 449 for early references). The results so obtained, in addition to providing anatomical data of prime importance, have opened new fields of knowledge although not necessarily contributing to the solution of the original problems.

Clearly, many of the difficulties are inherent in the nature of the brain itself where investigations are limited by complex structural and functional arrangements. It has become increasingly evident that areas of the cerebral cortex other than the so-called 'motor area' may be responsible for motor activities or participate in their regulation. It is very likely that integration of a normal behavioral pattern of movement results from the sum of several subliminal activities in groups of neurons which reciprocally influence each other at different levels in the central nervous system. Stimulation techniques potently emphasize the ease of disruption of the delicate balance between inhibitory and excitatory processes through which the firing of neurons is regulated. On the other hand, ablation is of little assistance here since cortical resection results in functional changes which can rarely be construed as the inverse of the effects of stimulation.

It might, therefore, be considered that the coordinated action of structures involved in sensorimotor activities is very easily disrupted when submitted to these experimental procedures and that the experimenter sees only a distorted view of the original processes. We might, thus, conclude with Sherrington (394) that "our expectation must be modest, for modest assuredly must be the achievement reached by such means in a problem of such a nature."

A further difficulty in assessing cortical motor functions arises from the current practice in clinical terminology of identifying the upper motoneuron syndrome as a 'pyramidal' one in contrast to the 'extrapyramidal' syndromes. Historically, the development of this terminology, and of the related concept of two separate systems involved in motor functions, arose in the observation that motor disorders of particular types result from lesions elsewhere than in the pyramidal tract. Reappraisal of this concept of a double motor system has been necessary (cf. 196, 303, 325–328) with the acquisition of anatomical and physiological data to be presented below and by other authors in this work. Briefly, it must be conceded that when the term 'upper motoneuron syndrome' is used and account taken of a simultaneous involvement of extrapyramidal functions, a distinction can be drawn between this syndrome and those which are primarily extrapyramidal in origin. This concept appears to have a firm basis in clinical and experimental observations. Skilled movements are abolished in primates, including man, by lesions in the so-called 'motor' area as well as by lesions which involve, partially or totally, fibers coming from this area and traveling in the pyramidal tract. Two facts, however, are clear. *a*) Both initiation of movements, using the term 'initiation' in a purely mechanistic sense, as well as their control require adequate information from proprioceptive and exteroceptive receptors. The patterning of a behaviorally appropriate sequence of movement is possible only with a background of information provided from these inputs (45, 141, 336). *b*) The coordination of tonic and phasic activities in the participating muscles as well as all necessary adjustments in posture, including muscles other than those primarily involved, results from integrated activity in all participating structures (pyramidal, extrapyramidal, cerebellar and spinal). Additionally, there are probably concomitant changes in the autonomic sphere.

The cortex is obviously one of the places where regulation and modification of an initiated movement can occur through convergence here of all relevant information in a structure which is capable of great integrative functions, and which in turn can influence the effector apparatus via the pyramidal tract and by acting upon subcortical structures which mediate extrapyramidal motor effects. Stimulation of the primary motor cortex, after section of the pyramidal tract (cf. 421, 422), is followed by synergic movements which were interpreted as 'significant' acts, even if limited to the proximal segments of the limb (422).

For this reason, a distinction between pyramidal and extrapyramidal activities contributing to motor functions at the cortical level becomes quite arbitrary. In addition, experimental and clinical findings can demonstrate only predominance of function or functions, but they can rarely exclude the coexistence of other functions. We shall, therefore, attempt a description of the role of the cortex in sensorimotor activities without pretense to a rigid scheme of organization.

COMPARATIVE STUDIES OF EXCITABLE CEREBRAL CORTEX

Historically, since the earliest experiments of Fritsch & Hitzig (158) a formidable body of data has been gathered on the arrangement of cortical zones from which somatic movements can be elicited by electrical stimulation or by application of drugs (31, 32, 186, 223) to the cortical surface. With increasing sophistication of electronic techniques, many of the problems associated with control of stimulus parameters have been solved, but the probability of current spread to areas remote from the site of stimulation has continued to beset investigations in this area and may be responsible for many seeming inconsistencies. In their experiments, Fritsch & Hitzig (158) and Hitzig (205–207) used bipolar galvanic stimulation. In 1873, Ferrier (143) introduced faradic stimulation as preferable to galvanic stimulation. Although in his hands the movements were less discrete than those described by Fritsch & Hitzig and were evoked from wider areas of cortex, refinements in the faradic technique led to its general acceptance. A logical extension of this method has been the application of square-wave and other pulse trains under carefully controlled conditions (see below).

Phyletic Aspects of Cerebral Cortical Representation

The progressively augmented complexity in the cortical motor representation of body regions seen in the higher mammals may be assessed by the increasing intricacy of motor patterns elicited by cortical stimulation in higher primates, including man, and by the severity and persistence of motor defects after cortical resection in the primates as compared with lower mammals.

It must be emphasized that cortical stimulation with trains of pulses or sine waves has failed to elicit anything but fragments of skilled movements. The relatively crude nature of these responses may well arise from the inability of artificial stimulation to simulate the natural patterns of cortical excitation. The progressive incorporation and elaboration of motor functions at the cerebral cortex may be correlated, too, with the relative and absolute increase in the size of the responsive areas in man and higher apes, and with the increasing differentiation of the microscopic arrangements of the motor cortex, both in the volume of the dendritic field of individual cells and in the laminar organization of the cortex as a whole.

In reptiles, such as the alligator, turtle and lizard, the formation of the motor cortex is foreshadowed (29, 30, 222). In these forms, the axons of the stimulable cortical cells do not form a corticospinal tract; this makes its first appearance in mammals (226).

In the monotremes, Martin (291) found a large, ill-defined responsive area on the anterior half of the lateral surface of the hemisphere of the platypus. There was a large face area with forelimb responses from the same region at a higher threshold. No hind-limb movements were evoked. The marsupials also showed a poor separation of face and forelimb representations. Hind-limb representations tended to be inconstant and movements diffuse (1, 145). Even in the higher marsupials, such as the kangaroo, hind-limb responses were not elicited in some animals (437). Huber (212) suggests that, in the evolution of their motor cortex, the marsupials have not reached the stage where their hind-limb representations are stably represented in the cortex, and that the response variations noted may reflect individual variations in the degree of representation. Since in the marsupial, at least, maps of the excitable areas indicate movements from regions forming parts of the somatic sensory cortex, the possibility must also be considered that movements are evoked in response to a sensation (5) rather than as part of a primary motor response.

Turning to the placental mammals, it would not seem fruitful to review extensively at this point the numerous studies of cortical motor functions in lower mammals since, at best, the knowledge so gained gives but a fragmentary picture of the motor organization in the total gamut of placental mammals.

Among the smaller mammals, including insectivores, bats and rodents, the excitable cortical areas lie close to the anterior pole of the hemisphere. Representation of facial musculature is more extensive than of other body regions in these animals, with representations of the snout muscles predominating over other facial zones in forms, such as the hedgehog, where the snout plays a major functional role (288, 437). Limb responses tend to be meager, with overlap between forelimb and hind-limb areas. Hind-limb responses are elicited at higher thresholds than those from the forelimb and have not infrequently been reported as absent. In the ungulates, limb representations have likewise been difficult to evoke, even with stimulation under local anesthesia (28, 397).

In the carnivores, the excitable areas are grouped around the cruciate sulcus. In these animals a greater complexity of cortically induced movement parallels increasing histological differentiation. Facial and forelimb areas are clearly separated and contralateral

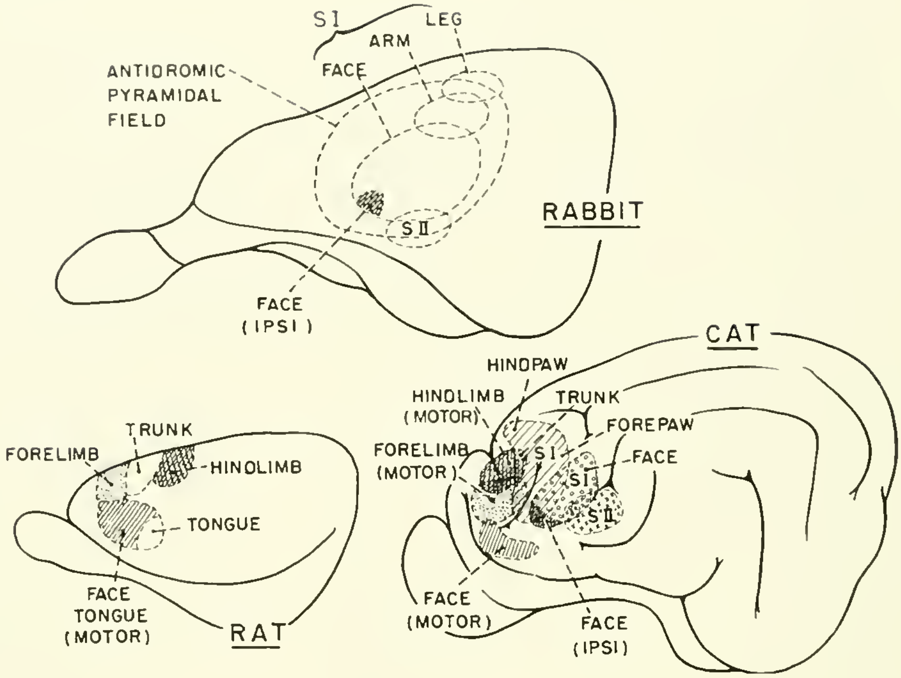

FIG. 1. Motor and sensory representations in the cerebral cortex of rabbit, rat and cat. In the rabbit, the subdivisions somatic area I (*SI*) and somatic area II (*SII*) are overlapped to a great extent by the responsive field to antidromic stimulation of the medullary pyramid. The map for the rat shows motor representations only. [After Brodmann (64), Gulotta (186), Huber (212), Woolsey & Fairman (477), Adey & Kerr (5) and Porter (365).]

hind-limb movements readily obtained (143, 158, 249, 348, 349, 443, 470). Much of the excitable cortex in the carnivore is buried in the cruciate sulcus, and specific attention has been directed to this problem by Stout (413) and others, and more recently by Delgado (116). Leyton & Sherrington (266) had estimated the buried cortex in the higher apes at about 35 per cent of the whole motor region. In the cat, Delgado found that the buried cortex in the cruciate sulcus contains a motor representation of the hind limbs, whereas forelimbs, neck and face are consecutively placed from the superior to the inferior part of the presylvian sulcus.

The primates have a common general plan of cortical motor organization, exemplified by the arrangement found in the monkey, as shown in figure 2. Although motor functions may be ascribed, with good reason, to a variety of cortical areas, including certain parts of the temporal and occipital lobes, it would seem useful as a point of departure to focus attention on the three cortical zones from which motor responses can be elicited in the greatest profusion and complexity. The nature of the responses from these areas will be discussed below.

An area of the frontal lobe lying in front of the central sulcus in gyrencephalic brains forms the Rolandic or precentral motor area. This strip, with a vertically inverted and sequential representation of body parts, may be considered as a unit jointly with a similar but less powerful motor representation in a parallel strip of postcentral cortex yielding weaker and less discrete motor responses. Its representations are essentially contralateral (cf. 357, 482). There is a progressive phyletic increase in the representation of distal segments of the limbs, with a remarkable expansion of the digital representation.

At its upper end the Rolandic area adjoins the medial border of the hemisphere, and in man the contralateral foot is represented on the medial aspect of the hemisphere in the paracentral lobule. In this region the Rolandic area adjoins a supplementary motor area. As noted by Munk (339) and by Horsley & Schafer (211), stimulation of the cortex within the longitudinal fissure anterior to the primary leg representation in the monkey produced movements of the contralateral arm and head turning. Grünbaum & Sherrington (184) noted movements of foot and leg, shoulder and chest, thumb and fingers from stimulation in this area in anthropoid apes. They considered that the conditions under which these reactions occurred separated them from those characterizing the Rolandic 'motor' area. Studies to be reported below (358, 479–481) have indicated a largely bilateral representation of body parts in this supplementary area.

The third cortical zone which may be involved in integration of movements is the second somatic area, located in the monkey on the superior lip of the lateral

sulcus (357, 358, 414) and extending to the insula. Movements of the face and limbs were evoked from this area and were in all cases contralateral.

Of the higher primates, the orang was the first to be explored (43) and showed an extension of the excitable cortex into the postcentral gyrus. Later, Grünbaum & Sherrington (184, 185) stimulated seven other great apes, including the orang, chimpanzee and gorilla. In contrast to Beevor & Horsley (43), they found that the electrically responsive area occupied the whole length of the precentral convolution and, in most places, the greater part of its width. They noted a downward extension almost as far as the fissure of Sylvius and medially into the paracentral lobule. Only feeble responses were seen from the postcentral gyrus. Localized movements were more readily obtainable in these apes than in the monkey (199, 394).

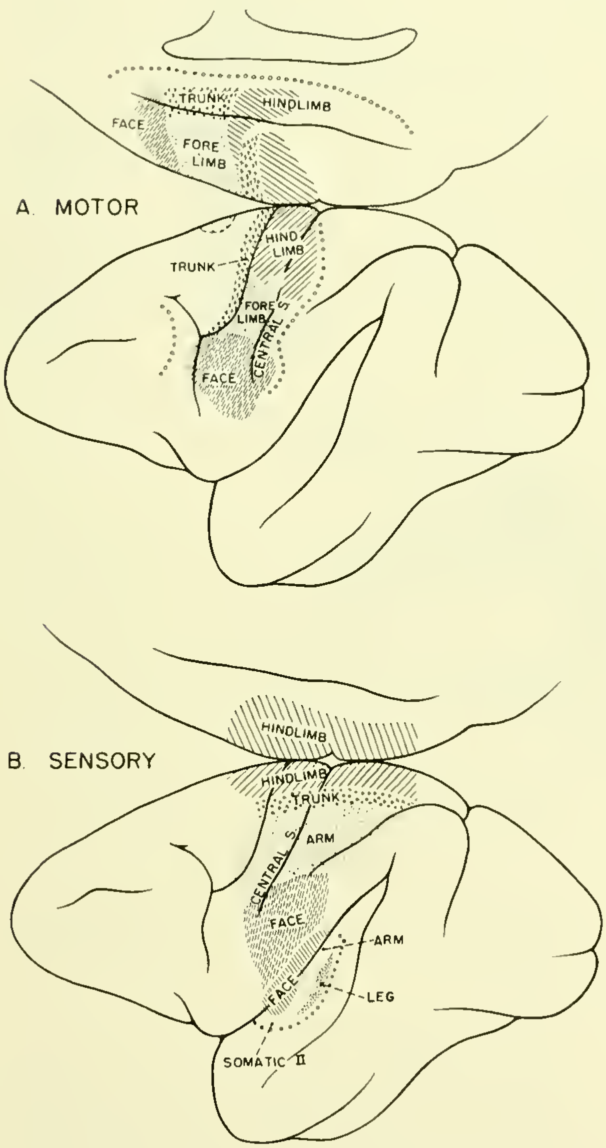

FIG. 2. Motor (*A*) and sensory (*B*) representations in the monkey. The medial aspect of the hemisphere is depicted as adjoining the dorsolateral aspect. In each map the depths of certain sulci are indicated by *lines of open circles*. Thus, the supplementary motor representation extends into the superior lip of the cingulate sulcus. Somatic area II extends into the superior bank of the Sylvian fissure. [After Woolsey *et al.* (478), Woolsey & Fairman (477), Malis *et al.* (287), Adey *et al.* (8) and Travis (426).]

Sherrington and his colleagues subsequently examined the 'echo responses' elicited from the postcentral gyrus (266). Strong faradization of the postcentral cortex in anthropoid apes produces only weak movements. Brown & Sherrington (68) showed that stimulation of the postcentral gyrus immediately following cessation of precentral stimulation leads to responses resembling those elicited from the precentral gyrus, but that this response fails after the first or second stimulation. However, by applying liquid air to the precentral cortex, Graham Brown (67) established that these effects from the postcentral gyrus are not due to spread of current to the corresponding section of the precentral gyrus. Brodmann (63) and Vogt & Vogt (437) had previously noted that destruction of the postcentral gyrus in the monkey led to a decrease in the adequacy of movements.

Human stimulation studies date from 1874 with the attempts of Robert Bartholow in Cincinnati to evoke movement in a patient in whom the brain was exposed through a suppurative condition of the scalp with the aid of an electrostatic generator (40). The unfortunate outcome of his experiments was a deterrent to further investigation for some years. Keen in 1888 reported three successful cases of faradic stimulations (227). Lamacq (245) and Krause (235, 236) also employed unipolar faradic stimulation, and in 1905 Mills & Frazier (315) described the position and subdivisions of the human motor area with a view to surgical intervention. Cushing (109) and van Valkenburg (430) applied techniques of local anesthesia to permit stimulation of conscious patients. They observed a differentiation of sensory and motor functions at the central sulcus. Foerster (148, 149) explored the cortex in epileptic patients, using galvanic stimulation with local anesthesia and faradic stimulation under general anesthesia, and found excitable zones outside area 4, including areas 3, 1 and 2 of the postcentral gyrus.

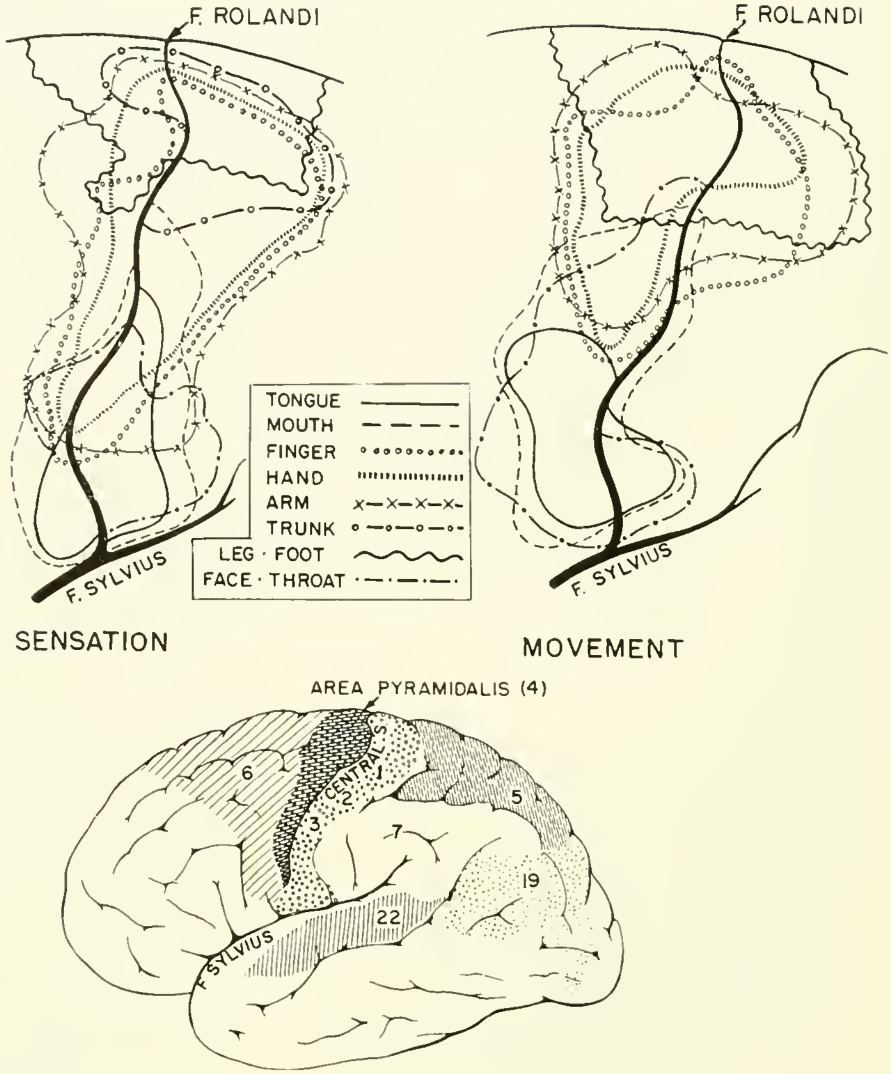

FIG. 3. The sensory and motor representations in the human brain as determined at operation, indicating the extent of overlap between various body regions. The *lower figure* indicates the cortical zones yielding motor responses. The *numerals* designate Brodmann areas within the responsive zones, but the limits of these zones are not coincident with histologically defined cortical areas. The supplementary motor area on the medial aspect of the hemisphere is not shown. The anterior part of the *shaded region* including area 19 has been described by Penfield and Rasmussen as concerned with arrest of speech, while the posterior part of this zone has been shown to be involved in associated adversion of head and eyes, although in Penfield's view these responses are seen more frequently from an epileptic focus here rather than from cortical stimulation. [After Foerster (150), Penfield & Boldrey (356) and Rasmussen (358).]

The work of Penfield and his colleagues, summarized by Penfield & Rasmussen (358), has greatly extended our knowledge of the closely woven patterns of the human motor cortex. These studies have emphasized the motor responses in the hands, lips, vocal cords and jaw which can be elicited from the postcentral gyrus and the extent of the supplementary motor area on the medial aspect of the hemisphere. The sensory and motor areas are shown in figures 3 and 4.

Certain phyletic aspects of cortical differentiation in the primate will be discussed below in relation to the Babinski response. Much additional information will be found in the reviews of Hines (199), Bucy (73) and Woolsey *et al.* (481). Before presenting a detailed discussion of stimulation and ablation studies in the cortex, ontogenetic aspects of motor functions will be outlined.

Ontogenetic Development of Motor Cortex

Although the motor facial area was one of the first in the phylogeny of mammals to become definitely localized in the cerebral cortex, in ontogeny the facial area of the subprimate becomes responsive to electrical stimulation at a considerably later stage than does the forelimb area (212).

Weed & Langworthy (470, 471) and Langworthy (248, 249) stimulated various stages of the pouch-young of the marsupial Virginian opossum (*Didelphys virginiana*), corresponding to early fetal development in placental mammals. At 23 days, with a crown-

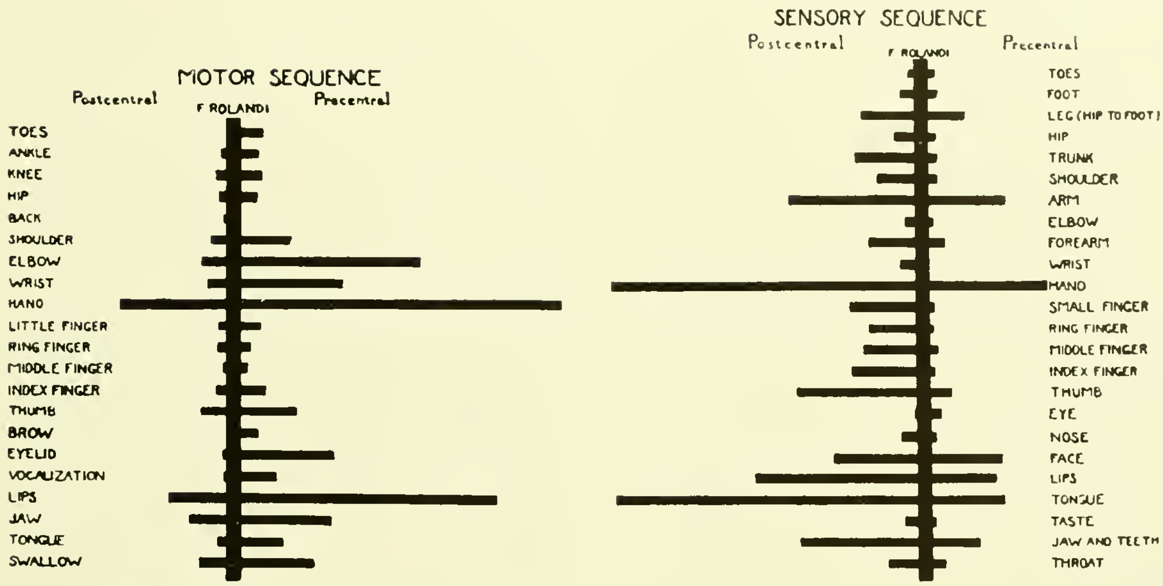

FIG. 4 Motor and sensory sequences in human pre- and postcentral gyrus. This scheme of representation does not take into account the considerable overlap of body parts depicted in figure 3. [From Penfield & Boldrey (356).]

rump length of 33 mm, forelimb movements followed cortical stimulation, but other body regions remained unresponsive. In these animals birth occurs after a 10-day gestation period, and the immaturely born young (crown-rump length, 11 mm) crawls to the pouch, using the forelimbs and swaying the head as far as possible to the opposite side to the propelling hand (189). Movements of the face appear next but cannot be obtained by stimulation until the 76th day. Huber suggests that precedence in structural development and early use of the forelimbs arises here in connection with the neonatal processes peculiar to the marsupial and not as part of a phylogenetic developmental sequence (212). No hind-limb movements were seen by these observers from cortical stimulation of any stage of the pouch-young opossum nor from a larger series of adult opossums.

In the placental mammals, newborn and very young specimens of cats, dogs, rabbits and guinea pigs have been studied. Most of these studies are to be found in the older literature which has been reviewed by Huber (212). Stimulation has yielded varying results (120, 247, 249, 311, 316–318, 348, 349, 407, 443, 470). Mills (318) found that for several days after birth the cortex of the cat was unresponsive to electrical stimulation under ether anesthesia, but that in some cases it was functionally active before the eyes opened, about the 9th day. Centers for the forelimbs responded earlier than those for the hind limbs, and head movements appeared at a later date than movements of the limbs. In similar experiments in newborn kittens (249) forelimb movements were seen, however, but movements of the hind limbs were not obtained until the 16th day, and facial movements at 21 days. Soltmann (407) observed a similar sequence in dogs under ether, chloroform and morphine. In large dogs, cortical motor centers may become functionally active at a later date than in small breeds, such as terriers (212).

CORTICAL STIMULATION STUDIES OF ROLANDIC MOTOR AREA

The selection of the optimal parameters of electric stimulating currents has long exercised the interest of physiologists. Wyss & Obrador (483) emphasized the relation between the pulse duration of the stimulating current and the threshold for various types of movements produced by cortical stimulation. Frequency, wave form and pulse duration are all intimately involved, apart from such additional variables as electrode configuration and spacing, and type and depth of anesthesia. These problems have been studied particularly with respect to the responses elicited from the Rolandic area. As indicated in the maps of

Penfield, Woolsey and others, there is a significant distortion in the relative size of body parts when represented in the form of a "homunculus." However, such a method of depicting the cortical representation must be treated with reserve by reason of the great overlap in the responsive zones found at any one point.

Using sine wave monopolar stimulation of the precentral gyrus of adult chimpanzees at frequencies from 5 to 1440 cps, Hines (201) found that the optimal frequency for eliciting movements was around 90 cps. She observed jerky uncompleted movements at frequencies from 1260 to 1440 cps. Delay in the onset of the response was related to both stimulus intensity and frequency. The delay at liminal or supraliminal intensities was longer for low frequencies than for high frequencies. Boynton & Hines (53), in similar studies with sine wave stimulation in cat and monkey, had previously observed two optimal frequencies (80 to 120 and 500 to 600 cps). Exploration of the cortex in depth indicated a drop in threshold from 3.0 v. at the surface to 1.0 v. in layer V. Brown & Blackett (66), in studying motor responses to subcortical stimulation, have confirmed that the delay in the onset of motor responses is related to the intensity of the stimulus. Adrian (9) has pointed out that stimulation of the cortex at one-half to one-third the movement threshold is sufficient to evoke a negative potential for a distance of 2 to 4 mm around a unipolar electrode. Cortical unit studies in relation to motor responses will be described below.

McCulloch (294) has indicated that increasing duration of the stimulating pulse leads to excitation of an increasing proportion of the motor neuron pool. There is, of course, a limit to the duration of rectangular pulses which may be applied without risk of cellular damage. For this reason, Lilly *et al.* (274, 275) have investigated the use of a differentiated square wave with an invariant period between the positive and negative phases. They claim that this form of stimulus does not detectably injure cellular function when passed through the cortex at strengths near threshold 4 to 5 hours per day for 5 to 15 weeks, and suggest that other similarly balanced brief wave forms might be expected to produce equivalent results.

Cure & Rasmussen (106) have investigated the separate roles of frequency, wave form and pulse duration, as well as intensity, on motor responses in the macaque. They used bipolar silver electrodes with a tip separation of 2 to 3 mm, and pulse durations of 0.1 to 3.0 msec. at frequencies of 2 to 200 per sec. A burst of stimuli was delivered for 1.2 sec., once each minute. Under these conditions, they observed from many points reproducible changes in motor responses directly attributable to alterations in frequency. These effects were more often seen from points near the junction of primary areas of representation, or from those areas usually assumed to represent more proximal muscle groups of the extremities. Thus, stimulation of a point in the 'arm' area near its junction with the 'face' area produced only thumb responses at voltages of threshold intensity when the frequency was less than 30 per sec., and only lip responses at frequencies above 30 per sec., with voltages at or near threshold. Farther medially in the thumb area, high frequencies often produced movement of more proximal muscle groups of the extremity, either alone or with thumb movement. Thumb movements occurred at stimulus rates of 2 to 30 per sec., while with frequencies from 6 to 150 per sec., wrist extension occurred, either alone or with thumb movement. These investigators prepared three separate response maps at 2 to 10, 60 and 200 stimuli per sec. The high frequency map was characterized by a paucity of toe, thumb and finger movements. The order of motor sequence was identical in each, and the boundaries between face, arm and leg subdivisions, as determined by these threshold stimulations, were almost identical. Similarly, stimulation of the frontal eye fields in area 8 has produced conjugate deviation of the eyes with brief pulses at 50 per sec., but at 10 to 20 per sec. ipsilateral deviation occurred (278). From the upper part of area 8, a 'waking' reaction in eye movements occurred at high frequencies and a 'sleeping' response at low frequencies.

The consequences of altered pulse duration have also been studied by Cure & Rasmussen (106). Usually motor responses at a given frequency were the same over the range of durations tested (0.1 to 3.0 msec.). Occasional reproducible alterations were seen which seemed to be correlated with alteration in pulse length. Thus, at one cortical point pronation of the proximal forelimb with 3.0 msec. stimuli changed to finger movements with shorter stimuli (0.1 to 1.0 msec.) at 30 stimuli per sec. Longer pulse durations would fire cells more peripherally placed. A fortuitous placement in relation to the neuronal foci for the pertinent muscle groups, as postulated by Chang *et al.* (88), might permit such an alteration of response as varying groups of cells were activated.

The effects of increasing intensity of stimulation have been variously reported. Clark & Ward (92) found that occasionally strong stimuli might produce a different pattern of response in which the movement elicited by weak stimuli did not occur or was com-

pletely masked by other stronger movements. For example, fanning of the toes occurred at an intensity of 1.0 v., while with 1.4 v. no fanning of the toes occurred, but violent flexion of the knee and hip was elicited.

Murphy & Gellhorn (341) found by direct measurement that spread of current was probably a negligible factor in spread of additional movements at higher stimulus intensities. They incised the cortex between two points representing shoulder and thumb areas and inserted an insulating sheet into the incision. The original responses from these two points still occurred. Moreover, differential responses elicited from the 'shoulder' point, with high and low frequencies producing separate shoulder and thumb movements respectively, were still present after the incision. The same changes of motor response with varying frequencies persisted on stimulation of white matter after removal of the overlying cortex, suggesting that integrative processes at subcortical or spinal levels or both may be important in producing these variations in motor response dependent on either pulse frequency or duration.

The part played by cells in different layers of the cortex in the initiation and maintenance of movement remains obscure, and unit studies bearing on this problem will be discussed below. It may be pointed out from thermocoagulation and depth studies that, while motor responses may arise from pyramidal cells in the deeper layers of the cortex, there is some evidence that superficial cellular layers are also involved (53, 124). Dusser de Barenne & Marshall (128) showed a definite lowering of the threshold to faradic stimulation when 1 per cent procaine was painted in a circle around the point stimulated and suggested that there was a release of this point from inhibiting influences of surrounding cortex.

It has long been recognized that motor responses from the cerebral cortex may involve inhibitory as well as excitatory effects (70). Bosma & Gellhorn (52) noted decreased firing in the electromyogram during cortical stimulation and the direct visual observations of Clark & Ward (92), Cooper & Denny-Brown (101), Sherrington (394) and Cure & Rasmussen (106) revealed that subliminal stimuli, insufficient to produce an active movement, elicited an obvious relaxation of the tonically contracted extremity. Raising the stimulus considerably above threshold produced stronger and additional movements. Instances of simultaneous contraction of antagonistic muscles were not observed either during cortical stimulations (192) or when the stimulus was applied to the white matter (191).

Nature of Cortical Representations

Turning to the question of the nature of the cortical motor representation of body regions in the cerebral cortex, one is immediately faced with the problem as to whether individual muscles achieve a representation in the precentral strip, or whether the representation is of groups of muscles concerned in patterned activity necessary to the performance of movement. The issue has been vigorously debated and admits of no easy solution. Moreover, studies in unanesthetized animals indicate the possibility of evoked motor responses from widespread areas of the cerebral cortex (276, 277).

Walshe (462–465) has argued that whenever a reaction is evoked from stimulation of the motor area, it is an organized pattern of response involving reciprocal innervation of opposing muscle groups and not merely the reaction of a single muscle or part of a muscle. The opposite point of view, namely that individual muscles may be activated by appropriate stimuli, has been vigorously championed by Fulton (161) and others. Chang *et al.* (88) isolated eight muscles and showed that, at certain cortical points, threshold stimuli evoked 'solitary responses', i.e. an isolated reaction of a single muscle. In some of the larger muscles, separate groups of fasciculi within a particular muscle mass were individually stimulable, and they concluded in consequence that at some level "muscles must be represented as muscles" so that they can be manipulated and organized into movements.

At least a partial solution to this intellectual impasse has been offered by Liddell & Phillips (269–271), who noted the change in the baboon's cortex from the map of few effects and extensive responsive areas elicited by single shocks to the map of many effects and narrow areas delineated by repetitive stimulation at 50 per sec. The latter grows into the traditional map of 'motor points.' They agree with Walshe that Jacksonian fits have their characteristic form of onset because the movements concerned are those that have the widest fields of low threshold. In further studies of the motor cortex in the baboon, with single shocks 1 to 5 ma in strength and 5.0 msec. in duration, they elicited flick movements of thumb, index and minimus, of the hallux and other toes, of the tongue and angle of the mouth, centered on the middle, medial and lateral thirds, respectively, of the

precentral gyrus. The thumb complex had the lowest threshold, the face complex the highest. Increasing the frequency of stimulation dissolved this simple pattern of representation into the classical motor map. They have examined the cortical representation of motor units of the first dorsal interosseous muscle of the hand, with a view to testing the degree of unvarying inevitability or of causal lability of transmission along this neural pathway. They conclude that neither of these events is absolute and both obtain partially. Motor units in the first dorsal interosseous muscle were activated by single pulse stimulation of different motor points. Responses were variable with units fluctuating in latency and order of firing or not firing at all, and there was no more than a tendency to absolute or rigid relationships between any cortical point and a responding spinal motoneuron. The evidence suggested, however, that certain motoneurons may be summoned into action with special ease.

Liddell & Phillips (271) found no systematic lengthening of latency of motor unit responses from the center to the periphery of the cortical area, suggesting that there need be, as a rule, no additional synapses on any horizontal path running from the periphery to the middle (or low threshold part) of the stimulable cortical area. They consider their findings consistent with the view that the neural path from cortex to spinal motoneurons arises from all parts of the cortical area stimulated and not only from its lowest threshold part.

Autonomic Concomitants of Cortical Stimulation

Brief reference may be made here to the autonomic effects which follow stimulation of the motor areas of the cortex, since there is evidence that they may be mediated through fibers of the pyramidal tract (89, 246, 329, 382). If limb and kidney volumes are simultaneously recorded during stimulation of area 6 in the monkey, limb volumes increase while kidney volumes diminish. There is also a sharp rise in systolic arterial pressure which is independent of limb movements since it is seen in the curarized animal. This shift in blood volume is from viscera to muscles, rather than from viscera to skin (182, 210).

Vasodilator responses follow stimulation of the motor cortex of the dog in an area between the cruciate sulcus and the sulcus considered to be homologous to the fissure of Rolando (139), and subcortical vasodilator points seen in these experiments may indicate the participation of a corticohypothalamic pathway with at least some fibers passing in the internal capsule to the anterior hypothalamus where relays descend to lower levels. Lund (284, 285) has described an analogous autonomic response in the cat where very active vasoconstrictor reactions can be obtained from the frontal pole from an area corresponding closely with that outlined by Rose & Woolsey (378) as the orbitofrontal projection area of the dorsomedial nucleus of the thalamus. Vasoconstriction is confined largely to the skin and is accompanied by a rise in the systolic arterial pressure. Lund suggests that in view of the overlap of the vasomotor and the motor centers of the cortex, voluntary muscular work constitutes the normal physiological stimulus for the cortical vasomotor center, and that specific autonomic foci may share a representation with appropriate somatic areas.

Little is yet known about the anatomical pathways mediating these autonomic effects, although the physiological evidence suggests that cortical influences relay in hypothalamic and mesencephalic nuclei, in addition to more direct pathways through the pyramidal tract. Eliasson *et al.* (139) have drawn attention to the finding that cortical stimulation affects particularly the sympathetic vasodilator outflow, and that this is apparently concerned solely with the integrative control of muscle blood flow. Direct stimulation of the hypothalamus mimics in many respects the autonomic responses to cortical stimulation, with redistribution of splanchnic blood to active muscles in a fashion consistent with the role assigned to the hypothalamus in response patterns of emotional arousal in emergency situations.

The results of cortical stimulation suggest that these cortical vasodilator neurons are concerned primarily with the initial adjustment of muscle blood flow during exercise and occur with such speed that a neural rather than a humoral mechanism is necessarily involved. It is further postulated that these sympathetic vasodilator nerves may be involved in the control of muscle blood flow even if the organism is not under stress. Although the sympathetic vasodilator nerves may play a part in the initial rise of blood flow in the muscles at the start of muscular exercise, they are not necessarily involved in the regulation of muscle blood flow during exercise. Nevertheless, some difficulty attaches to the interpretation of the apparent absence of tonic effects of cortical volleys on the vessels of skeletal muscles since most observations have been made in animals under general anesthesia. This topic is discussed at length by Uvnäs in Chapter XLIV of this work.

CORTICAL ABLATION STUDIES OF ROLANDIC MOTOR AREA

The neurological deficit following resection of cortical motor areas becomes greater at progressively higher levels of the phylogenetic scale. Walker & Fulton (459) have examined the effects of hemidecortication in carnivores and a series of primates, including the monkey, baboon and chimpanzee. Whereas the hemidecorticated cat is able to walk on the first postoperative day, this operation produces severe paralysis with persistent paralysis and reflex changes in higher primates. Walker & Fulton discuss two possible explanations for these differences. Either there is greater bilateral motor representation in the lower animals or there is greater encephalization of function in the primates. Although there is evidence for the ipsilateral control of movements in rabbits, cats, dogs and monkeys, an extensive comparative study is lacking; and Walker & Fulton conclude that the differences arising from hemidecortication are more probably attributable to increasing encephalization in higher mammals where the more extensive and more complex cerebral cortex may assume functions controlled at subcortical levels in lower mammals.

Phyletic differences in the degree of spasticity induced by cortical resection have been stressed by Walker & Fulton, and since this is a dominant aspect of the postoperative picture, a discussion of its mechanisms of origin will be found in Chapters XXXII by Denny-Brown, XXXIV by Patton & Amassian and XXXV by Jung & Hassler.

Removal of the excitable areas of frontal and parietal lobes in primates from monkey to man reveals the increasing significance of the role of the cortex in motor functions, both by reason of the increasingly profound paresis immediately after ablation in higher primates and also from the decreasing extent of ultimate recovery following such resections. Attention will be directed first to the effects following removal of the primary motor area.

Proceeding from earlier investigation (cf. 320, 321–324, 394, 449), Fulton & Keller (162) removed the foot area in the precentral gyrus of the young chimpanzee after defining its margins by faradic stimulation. A profound monoplegia ensued for 24 hours with complete areflexia, but the knee jerk then reappeared and with it a faint withdrawal response on vigorously pinching the plantar surface. By the second day the withdrawal response was more obvious. The paresis was at all times flaccid in the digits and remained so for 9 mos. Movement began to reappear at the hip after 4 or 5 days, followed by knee and ankle movements, but the digits tended to remain permanently paralyzed. Fulton & Keller then studied a series of other primates with lesions sharply restricted to the posterior part of area 4, including monkeys, baboons and gibbons, and confirmed the presence of a flaccid paralysis.

Denny-Brown & Botterell (118) made subtotal lesions of area 4 and found that muscles of the fingers may go through moderate spasticity in the course of recovery of motor power, even though more proximal muscles are flaccid. Travis (425) observed after precentral motor lesions in the macaque an immediate severe voluntary impairment, hypotonia and diminished tendon reflexes. No ipsilateral deficits were observed. In contrast to Fulton & Keller's findings in the chimpanzee, recovery was as rapid in distal as in proximal joints, with impairments persisting in both. Within 2 to 12 weeks these animals were able to pick up small stationary objects by apposition of thumb and index finger but never again at faster than half the initial speed. Atrophy of about 10 per cent appeared in contralateral limbs during the period of greatest disuse and completely disappeared after maximal functional recovery.

Lesions of the precentral agranular cortex in the macaque were found to interfere especially with skilled acts, as measured by time scores (369). Posterior lesions produced a greater defect than anterior lesions (the latter extending anteriorly to the arcuate sulcus). Visual discrimination and delayed response were unaffected. Bilateral ablation exacerbated the effects of a unilateral lesion. Pribram *et al.* (369) concluded that the motor defect in precentral ablation is not due to the loss of an act through excision of the locus of a 'habit', but rather that a scotoma of action results. Hopping and placing reactions (38, 475) and their abolition by lesions in the motor cortex are described elsewhere.

Much additional information is to be found in the comprehensive reviews of Hines (199, 203) and Penfield & Rasmussen (358).

Babinski Response

Historically, concepts concerning this sign have changed since the original proposals of Babinski (cf. 259) who noted that in certain patients with nervous system disorders, plantar stimulation caused an extension of the toes, especially the great toe, followed by abduction of one or more toes ('fanning'), and

that this appeared to result from a perturbation of function of the pyramidal tract. He recognized that the sign occurred in patients with intact pyramidal tracts, and that its anatomical basis might be obscure. Less cautious clinical observers have regarded the sign as pathognomonic of a lesion of the pyramidal tract. Nathan & Smith (345) examined the phenomenon following cordotomy and with histological control, and concluded that there is no relation between the anatomic state of the corticospinal tracts and the form of the plantar response.

Fulton & Keller (162) have investigated the Babinski response on a comparative basis in a series of primates. In the chimpanzee the reaction shows two phases, as in the human, with an initial digital extension, particularly in the great toe, followed by a phase of lateral deviation and fanning. The second phase is more obvious after bilateral removal of the foot areas and is augmented when the premotor area is encroached upon. The Babinski response persists indefinitely in the chimpanzee. In the gibbon, which they regard as intermediate between the baboon and the chimpanzee in encephalization, the Babinski response is well-developed for 3 weeks following area 4 ablation and then gradually disappears with the return of volitional use. Removal of the leg area on one or both sides of the motor cortex failed to produce the reflex in the macaque, mangabey, patas monkey or guenon. Only when the lower lumbar segments were freed completely from higher control by hemisection of the spinal cord was the Babinski response noted. In the baboon, on the other hand, removal of the cortical leg area produced the response, and motor recovery in the baboon was slower than in the monkeys. Fulton & Keller concluded that 'cortical dominance' is more highly developed in the baboon than in the other old world monkeys studied. The gibbon shows still higher cortical dominance, with an even more obvious Babinski sign, and an even slower return of motor functions.

Recovery After Ablation

The nature of compensation and recovery of function postoperatively has attracted considerable attention. A phenomenon of bilateral compensation for the effects of unilateral lesions of area 4 has been described, such that if area 4 of the remaining hemisphere is removed after a delay of 3 or 4 mos., none of the usual signs of pyramidal tract injury appear (2). Similar compensations occur in the absence of callosal connections but are prevented if the sensory cortex of areas 3, 1 and 2 are also removed. The premotor cortex may also participate in the process of compensation.

Kennard (230, 231) has studied extensively the influence of age on the processes of recovery of motor functions. The possibility of reorganization of these functions has been found to diminish progressively with age. While ablation of areas 4 and 6 in the infant monkey is followed by a quite substantial recovery, similar intervention in adult monkeys produces more dramatic and permanent motor defects. Participation of the intact cortex in the recovery processes has been postulated since ablation of either parietal areas 1, 2, 3, 5 and 7, or frontal areas 9, 10, 11 and 12 increases the pre-existing motor deficit. Murphy & Arana (340) found no evidence of reorganization in adjacent cortical areas after excision of the arm area. They suggest that the postoperative recovery of functions may involve subcortical mechanisms. Glees & Cole (177) have made repeated small lesions in the motor cortex of the macaque and mangabey. Small lesions of area 4 in the thumb and hand zones produced paralysis with a considerable degree of recovery and return of motor skill. Stimulation of adjacent cortex after recovery gave hand movements not previously present in these areas. Undercutting of these responsive areas caused a recurrence of paralysis and loss of motor skill. They consider that the motor cortex does not function as a mosaic but has a tendency, when a lesion occurs, to act in a less differentiated and more primitive manner which they ascribe to the plurisegmental connections of area 4 as revealed in their concurrent histological studies.

EFFECTS ON PHASIC AND TONIC MUSCULAR ACTIVITIES OF STIMULATION AND ABLATION OF CORTICAL AREAS OTHER THAN PRIMARY MOTOR AREA. THEIR CONNECTIONS

Supplementary Motor Areas

Following the early observation of movement from stimulation of the medial surface of the hemisphere (see page 800), the name 'supplementary motor area' has been applied by Penfield and his associates to this region within the longitudinal fissure in the superior and intermediate frontal region (358–360). A variety of responses follow stimulation here in man, including raising of the opposite arm, turning of the head, bilateral synergic contraction of the leg and trunk, movements of the eyes and pupillary changes,

cardiac acceleration, vocalization or arrest of speech (358). The movements of skeletal musculature were described as 'tonic contractions of postural type.' During epileptic attacks, arising from a focus in this area, similar tonic movements occur in which the whole body participates (357). Bates (41) found that stimulation of the medial aspect of the human hemisphere after hemispherectomy will induce movements of the ipsilateral extremities almost to the same extent as can be produced voluntarily.

The experiments of Woolsey and his associates (479–481) have provided a detailed description of representation of body parts within the supplementary motor area in the monkey. The face and arm portions of this area are in part on the free surface of the medial aspect of the hemisphere, and trunk and leg representations lie almost entirely on the dorsal bank of the sulcus cinguli. The lower face is nearest the rim of the hemisphere at the rostral end of the corpus callosum. The upper face, ear, neck and back as far as the tail are represented sequentially along the deepest part of the sulcus cinguli. Finger representations lie at the edge of the hemisphere at the rostral limit of the precentral motor area, while more proximal parts of the arms are activated from points between the finger area and the deeper parts of the sulcus cinguli. Leg points extend back on the upper bank of the sulcus cinguli with the proximal parts of the limbs situated rostrally and the digits caudally.

Unilateral ablation of the supplementary motor area in man does not produce a permanent impairment of posture or movement (359, 360) but only a transient and moderate hypertonia (360). Grasp reflexes follow unilateral or bilateral involvement (140). Travis (426) describes in the monkey grasp reflexes in the contralateral limbs after a unilateral lesion with moderate hypertonia but no noticeable paresis. Since after simultaneous bilateral ablation there is a greater resistance to passive movement and contractures have been seen (426), 'supplementary motor area' has been defined as a bilaterally functioning entity concerned with posture and movement (358, 426). Following bilateral ablation, no defect has been seen in the ability to perform simple and complex problems despite the difficulties from hypertonus accompanying bilateral lesions (188). Hopping and placing reactions are no longer present after a combined unilateral ablation of the precentral and supplementary motor areas (427).

There is no agreement as to whether the supplementary motor area acts directly, via fibers descending in the pyramidal tract, or merely influences the activity of other cortical or subcortical centers, or both. Movements have been described from stimulation of the supplementary motor cortex after removal of the precentral motor area and also in man after ablation of both pre- and postcentral cortex (357). Moreover, monopolar stimulation with single shocks in the supplementary motor area of the monkey is said to evoke a response of the pyramidal type (see Chapter XXXIV in this work by Patton & Amassian) in both ipsilateral and contralateral corticospinal tract (47). However, anatomical studies have not disclosed any degeneration of fibers in the spinal cord following ablation of a large part of the supplementary motor area, including resection of a point which yielded movements of the lower limbs (121; DeVito, J. L. & O. A. Smith, personal communication). Although these fibers descend in the internal capsule, the majority terminate in the pontine nuclei. A new series of experiments in the light of these anatomical findings has led to the conclusion that responses in the pyramidal tract can no longer be recorded after removal of area 4, if care is taken to prevent spread of stimulating current (403). When this possibility is avoided and area 4 is intact, it is found that the pyramidal tract responses to supplementary motor area stimulation have a longer latency than those from direct stimulation of area 4. This and other supporting evidence has suggested that the activity from the supplementary area is relayed through area 4 (403). Indeed, a large number of association fibers to this area has been observed histologically (121). Additionally, area 6 and the postcentral gyrus receive fibers from the supplementary motor area of both hemispheres (121). No projection to this area has been found from the nucleus ventralis lateralis thalami (14).

On the basis of these data, activation of area 4 through associational fibers, such as those from the supplementary area, might give rise to quite different patterns of movement from those which arise when the Rolandic motor strip is directly stimulated. It is obvious, however, that the complexity of motor patterns, including the homolateral movements obtained after hemispherectomy (41), must take into account the involvement of other cortical and subcortical structures which may be implicated on the basis of anatomical data cited above.

Second Somatic Area

Following the demonstration of the existence of a second sensory area by Adrian (10, 11), several studies have extended the concept of a somatotopic repre-

sentation within it (cf. 15, 54, 474). Evidence for the existence of such an area in man has been found also (357, 358). Some form of sensation, referred to parts of the lower or upper extremities, was produced by cortical stimulation in the region located on the superior lip of the lateral sulcus. These sensations frequently took, according to Penfield & Rasmussen (358), the form of a 'desire' to make a specific movement. From the same general area, stimulation has yielded both movements and inhibition of intercurrent movements. These results have been fragmentary and, according to Penfield & Rasmussen, the evidence does not yet justify the concept of an extensive and precise motor representation largely coincident with the second sensory area. In the monkey, however, such a motor representation has been described in detail by Sugar *et al.* (414). According to these authors, the somatic arrangement of motor points is roughly that of the second sensory cortex, which lies a little more posteriorly, overlapping this motor representation. The face region is anterosuperior and extends onto the lateral aspect of the hemisphere. The foot region lies posteroinferiorly. The hand region is by far the largest and lies between the other two. With stimuli at 4 per sec. movements were elicited with distal movements of limb parts greater than proximal. A separate second motor area, located posteriorly to the face area, has also been described by Garol in the cat (165). Ablation of the cortex, which in man would include the second somatic area, was not followed by either sensory or motor paralysis (358).[1] Intracortical connections of this area, as defined by strychninography (157), do not throw light on its possible functions.

Premotor Cortex (Area 6)

Architectural differences have led to the definition of the anterior portion of the agranular cortex as area 6 (cf. 444, 445). Rotation of the head and trunk to the opposite side, as well as synergic movement of flexion and extension of contralateral arm and limb, have been observed in man by stimulating area 6 after removal of area 4 (150). Contractions of proximal muscles of the extremities, as well as synergic movements, have also been seen in the chimpanzee (201). Interruption of both pyramidal tracts does not suppress the motor responses obtained from the macaque monkey. Those obtained from the anterior portion of area 6 were described as "flexor synergies with . . . grasping and deviation of the head and trunk to the opposite side" (cf. 204). It would appear, therefore, that movement evoked from area 6 might be mediated exclusively by extrapyramidal pathways. However, according to Foerster (150) and Fulton (161), some of them take place via the motor area as indicated by the effects of surgical section between these two areas. No discontinuity of responses between area 4 and 6 has been observed, however, by Clark & Ward (92) in the unanesthetized monkey. Changes in autonomic functions, induced by stimulation of this cortical region, are uncertain (232). Further information will be found in the works of various authors (160, 161, 204, 483) and in Chapter XXXV by Jung & Hassler in this work.

Lesions of the upper part of area 6 cause changes both of movement and of reflexes in the arm and leg (373, 374). A soft plastic rigidity appears with both lengthening and shortening reactions and a powerful involuntary 'grasp' reflex. The grasp reflex involves a slow flexion of the digits in response to contact with the palmar and plantar surfaces, and fluctuates in intensity with intercurrent visual and auditory stimuli. This reflex tends to disappear 2 to 3 weeks after a unilateral ablation but reappears in an exaggerated form following removal of area 6 in the second hemisphere. Bilateral resection of area 6 in the monkey is followed by severe defects in manual dexterity and postural adjustments.

Although a Babinski sign with extension of the great toe does not appear after a lesion in area 6 in the monkey, lateral deviation of the toes with 'fanning' is observed. Removal of area 6 secondarily to ablation of area 4 exaggerates these reflex disturbances with the appearance of the full Babinski response and a marked spastic hemiplegia.

The results of Jacobsen (218) indicate that area 6 plays a role in adaptive motor activities. Unilateral lesions do not impair fine adaptive movements but disorganize them as a pattern of response to a specific situation when assessed by trials with a problem box. However, recovery by postoperative training is possible. Some concept of the complexity of the interrelationships between pre- and postcentral motor areas may be gained from the studies of Welch & Kennard (472). Following ablation of areas 4 and 6 on the left side in an immature chimpanzee, a right

[1] In a paper by Orbach & Chow (347a), the performance of the rhesus monkey on six somesthetic discriminations has been tested after removal of sensory somatic areas I and II and areas 5 and 7 of Brodmann. Lesions restricted to somatic area II seemed to be without effect on these tests and do not exacerbate, even if combined with removal of areas 5 and 7, the loss which appears after lesion of sensory area I.

spastic hemiplegia appeared which resolved gradually and incompletely in the ensuing 5 years. Area 6 and part of area 4 were then excised on the right, leading to a left spastic hemiparesis and a transient accentuation of the paresis and spasticity on the right side. On subsequent ablation of the right postcentral gyrus, all extremities showed extreme paresis and spasticity which were more severe and persistent on the right. Further details are available (80, 204, 232).

Cingulate Gyrus

In view of the complexity attributed to the functions of the limbic cortex, reference should be made to Chapters LIV to LVIII of this work for a comprehensive review of the subject. Only those aspects of cingulate functions bearing on motor activities, and particularly those evoked from anterior cingulate areas, will be considered here.

Anatomical descriptions of the limbic cortex and its subdivisions in the rat (431), rabbit (377), cat (377) and primates (446) have been extensively reviewed (cf. 377) with attention to the phylogenetic aspects of this problem. Projections to this cortex from the anterior nuclei of the thalamus have been described (379; cf. 377). Corticocortical connections of the cingulate gyrus are far from completely understood. Strychnine neuronography has failed to reveal cortical association fibers to area 24 (294), but anatomical studies have described connections from the prefrontal cortex to the anterior cingulate region both in man and in monkey (cf. 7). The paracentral lobule may also have connections with the cingulate gyrus (240). A cingulate belt, lying along the lip of the cingulate gyrus and including also most of area 32 of Brodmann, has been considered to receive afferents from the 'suppressor strips' (35) and area 24 (123). Projections from area 24 to some portion of the precentral motor cortex, particularly area 6, have also been described (178, 468). There is evidence for projections from area 24 to the caudate nucleus (135, 294), anteromedial nucleus of the thalamus (342, 400), septal areas (178) and brain stem (cf. 466), but the last have not been confirmed (178). Other connections have been described between the cingulate and other parts of the limbic system (cf. 7), but their relationship to motor functions may be remote.

Although area 24 of Brodmann has been included in the so-called 'suppressor areas' (294, 295), the effects elicited by its stimulation are quite different from those said to characterize the phenomenon of 'suppression' (see below). Stimulation of cingulate cortex in acute experiments in the cat and monkey will alter cortically-induced movements in the direction of facilitation (224, 401, 469), of inhibition (208, 224, 237, 401, 404) or of facilitation reversing to inhibition (401). Anesthesia greatly modifies the observed responses (401, 469). Loss of muscle tone and abolition of deep reflexes also occur (404, 466). These stimulations produce irregular alterations in cortical electrical activity, which are not necessarily correlated with inhibition or facilitation of cortically-induced movement, suggesting that these effects may arise through subcortical mechanisms (401). However, according to Sloan & Kaada (401), some of the facilitatory effects might be mediated by corticocortical fibers.

In animals with and without anesthesia, gross, slow movements of tonic type have been observed to follow stimulation of anterior limbic cortex (198, 224, 225, 237, 466) which may result from 'downstream' influences at subcortical levels (198). Inhibition of spontaneous muscular activity has been seen with chronically implanted electrodes (401, 469), but these results are disputed (22, 91). Relationships with cerebellar mechanisms have been discussed (187, 263). Autonomic responses have also been reported, but these effects are variable and inconstant. This subject is discussed by Kaada in Chapter LV of this work.

Early experimental investigations of the effect of ablation in the cingulate cortex have been reviewed by Ward (466) who found no changes in motor control, deep reflexes, muscle tone or resistance to manipulation. A review of similar experimental results by other investigators, both in animals and man, is also available (343). Permanent involuntary grasping has been found after combined lesions of the cingulate gyrus and area 6 (374). Kennard (233) has described altered placing and hopping responses after bilateral anterior cingulate ablation. This would appear an isolated observation of involvement of the motor system. Kennard suggests that the hypomotility and inertia, said to occur both in monkey and man after cingulate ablation (cf. 368, 466, 467), may be regarded as a motor deficit or dyspraxia. The remaining aspects of the symptomatology which suggest the participation of the limbic cortex in the organization of patterns of motor performance in relation to behavior are discussed by Brady in Chapter LXIII of this work in connection with the possible involvement of limbic cortex in emotional functions (cf. 367, 368).

Parietal, Occipital and Temporal Cortex

Movements obtained by stimulation of the postcentral gyrus (areas 1, 2 and 3) have already been discussed (see page 801). Stimulation of parietal area 5 also produces movements as first observed in man by Bartholow (40). This finding has been confirmed both for man (149, 151, 439) and monkey (439), but some authors did not succeed in producing movement from this area (266). According to Dusser de Barenne *et al.* (126) movement of limbs is obtained, when facilitated, from both areas 5 and 7. The controversy seems to be settled by the comprehensive studies of Fleming & Crosby (147) and Peele (354). The first authors established that stimulation of area 5 produces motor responses of the head, trunk and extremities which are not discrete but often are combined and "resemble patterns of movements such as running, turning and avoiding movement of a given posture." These responses to stimulation were obtained also after ablation of both precentral and postcentral gyri in disagreement with other authors (cf. 147). Epileptic attacks can originate from area 5 with convulsive movements of the opposite arm and face and paresthesia (357).

Small lesions in the sensory cortex (areas 3, 2 and 1) of the macaque have been tested for their effects on discrimination by palpation, and associated effects on dexterity and motor power (100). In all cases, substantial or complete postoperative recovery occurred. Although these lesions were not associated with inability to make movements, they may have been accompanied by an initial unawareness of the movement made and with the limb then arrested in an unusual position. In all cases there was a loss of tactile sensation, with increased reliance on visual cues. Cole & Glees (100) identified intimate connections between areas 3, 1, 2 and 4 and consider that these cortical areas form a unit essentially linked with the thalamus and spinal cord but sending few fibers into areas either further anteriorly or posteriorly. Bender (44) has reported changes in sensory adaptation time and after-sensation with lesions in the parietal lobe. Peele (354) and Fleming & Crosby (147) have examined the effects of acute and chronic parietal lobe lesions in monkeys. Removal of area 3, areas 1 and 2 and areas 5 and 7 individually, or of areas 1 and 2 and 5 to 7 in combination, did not result in paralysis but produced a loathness to move. Removal of area 3 or of areas 1 and 2 affected the contralateral arm and leg equally. Removal of area 5 affected the leg particularly and of area 7, the arm particularly. Hypotonia persisted for as long as one year after operation and was greater in proximal than distal muscles. Tendon reflexes were permanently altered by an increase in threshold, a slowness of execution and an increased excursion. Muscular atrophy followed ablations of areas 1 and 2 and 5 to 7. Peele concluded that the postcentral cortex was essential for hopping and tactile placing reactions.

Movements of the limb, trunk and face have been observed following stimulation in the occipital cortex of primates (149, 211, 262, 439). Penfield & Rasmussen (358) do not mention, however, any motor responses from this cortical region. According to Brown-Sequard, confirmed in 1905 by Baer in an elegant experiment with chronically implanted electrodes, simultaneous stimulation of the motor area and of the occipital convolutions of the dog and rabbit leads to a lowered threshold in the occipital area with weak currents now producing movements similar to those obtained from the motor area (cf. 27).

Stimulation of the superior temporal gyrus has also been reported to produce movements of the extremities, head and trunk, both in monkey and man (151, 211, 262, 390, 439) even after ablation of the precentral motor cortex (484). They are different from those elicited from the amygdaloid nuclei. The latter are described in Chapter LVIII by Gloor in this work, while the role of amygdalostriatal interrelationships in motor functions is discussed in a recent review by Adey (4).

Phenomenon of Suppression

In 1919, Vogt & Vogt (438) reported inhibition of cortically-induced movements by stimulation of cortical regions in the frontal lobe. Since then, inhibitory effects on movement have been reported from stimulation of widely separated areas on the lateral surface of the cerebral cortex (194, 250, 375, 419–421, 424). In 1937, Hines defined a strip of cortex between areas 4 and 6 which yielded inhibition of muscular contractions of the opposite side of the body (200). Beginning in 1938, a series of publications on the effects of strychninization or electrical stimulation of certain points on the lateral surface monkey cortex indicated a decrease in the spontaneous cortical electrical activity, abolition of cortically induced movements and relaxation of muscular contractions (129, 130, 132, 134). These points were grouped as 'strips', designated 'suppressor areas' (33, 127), as

indicated in the maps of Bailey *et al.* (37). Functionally similar areas have been described in the cat (166) and comparable points noted in the human brain (168, 190, 347).

The phenomenon of 'suppression' was said to begin several minutes after stimulation, depending upon the depth of anesthesia and the distance of the stimulated point from the motor cortex, and to persist as long as 30 min. It was reported to be inconstant and variable, and could not be elicited again for a considerable period following the first response (cf. 122, 399). The postulated paths in this suppression were said to involve a corticosubcorticocortical circuit passing through the caudate nucleus (135). Corticocaudate connections were described by strychninography (131, 169), and corticocaudate fibers (cf. 321–324) were said to arise in the suppressor areas (176, 307) which, however, were not found by other authors (240, 433). Experimental findings indicated also that stimulation of the caudate inhibited cortically-induced movements (cf. 308) as well as depressed cortical electrical activity (174).

Much of the data relating to the phenomenon of 'suppression' has been challenged or reinterpreted (cf. 122, 399) with the implication that this phenomenon may not exist as a physiological mechanism. Sloan & Jasper (399) have identified 'suppression' with the phenomenon of spreading depression which is not restricted to specific cortical areas but is related to experimental interferences (cf. 122, 399).[2] In their study, and in that of Druckman (122), the available evidences are reviewed with the conclusion that the notion of 'suppressor areas' should be abandoned. Moreover, lesions of cortical and subcortical structures said to be involved in suppressor mechanisms have not produced an increase in muscular tone as would be expected in the concept of suppression. These data have been reviewed by Myers *et al.* (343).

In more recent years, however, a region in the superior temporal gyrus has been described as yielding phenomena closely resembling suppression both in man and monkey (152). While these results may eventually point the way to future research, at present it is obvious that the lability of cortical motor functions, as exemplified by both the facilitatory and inhibitory actions already discussed, suggests the existence of cortical areas capable of exercising a broad influence on the initiation and progression of movement. Such a function appears to be significant in the supplementary motor area, in area 24 and in the orbital cortex, but other cortical areas may participate, as suggested in particular by the studies of Tower (421) and Hugelin & Bonvallet (213, 215) discussed below. It is also interesting that reversal of the response to cortical stimulation may follow either alteration in stimulus parameters or repetition of the stimulus, although the mechanisms involved in this phenomenon are unknown. In this regard, it must be stressed that interruption or arrest of a given function by cortical stimulation, as in the arrest of speech or when a movement cannot be performed by the subject during the period of cortical stimulation (358), should not necessarily be considered as proof of the existence of an antagonistic action. Stimulation could merely interrupt a patterning of neuronal activity necessary for the performance of that particular function.

Ablation Interfering with Total Motor Activity

Hypokinesia follows lesions in inferior temporal cortical areas (261). It is a marked feature of ventral temporal resections in the baboon which involve mainly the entorhinal area, and partially ablate the hippocampus, but spare the amygdala on one or both sides (3). Carey (77) has drawn attention to the 'great loathness to move' in monkeys with lesions in the globus pallidus extending ventral from it and involving pathways from the orbital and more particularly from the temporal region. It may be relevant that pathways from the entorhinal area also traverse this region ventral to the globus pallidus in the marsupial (6). Both arrest of movement and automatic movements accompanying an amydgalostriatal interrelationship have been reviewed recently by Adey (4). See also Chapter XXXV by Jung & Hassler in this work.

Hyperkinesia, on the other hand, has been reported following lesions of the posterior orbital cortex in the primate with an increase in movement rates up to 600 per cent of that prior to operation (161). Certain aspects of the ceaseless pacing seen in these animals also accompany bilateral temporal lobectomy in the monkey, and a re-examination of objects handled only a few minutes previously may be repeated indefinitely without apparent cognition. These findings suggest that corticifugal influences from frontal and temporal areas may play on common subcortical motor mechanisms.

[2] A comprehensive review of literature relevant to spreading depression has appeared (289a).

Motor and Sensory Functions Persisting After Hemispherectomy

Dandy (110) was the first to perform hemispherectomy. This intervention in adults with hemiplegia of long standing, or in cases of infantile hemiplegia (241), produces no further increase in motor deficit. Cases published in the literature have been summarized (180) and a recent monograph in this subject is available (244). Briefly, when the hemispherectomy is carried out with the intent of leaving most of the basal ganglia, thalamus and hippocampus intact, the recovery of walking is rapid and some global movements of the opposite half of the body are present (183). The improvement in motor performance reported in some of the cases has been attributed to the reduction of spasticity which frequently follows hemispherectomy. The Babinski sign may be present or absent. The sensory status varies from subject to subject but, while the gnostic sensibilities are abolished, some gross, superficial and deep sensations, which usually have a painful component, are still present.

In the case of more nearly total hemispherectomy, as the ones performed originally by Dandy (110) which included the ablation of the head of the caudate nucleus and probably indirect alteration of vascular origin in thalamic and subthalamic centers, walking movements were never possible. Impairment of motor functions following hemidecortication were discussed by Walker & Fulton (459) in relation to the phyletic aspect of the problem. Other clinical and experimental findings will be found in the monograph cited.

MAJOR AFFERENTS TO CORTICAL AREAS CONCERNED IN SENSORIMOTOR INTEGRATION

Thalamic Afferents

The studies of Minkowski (320, 321–324) appear to have been the first experimental attempt at a systematic analysis of the connections of cortical precentral and postcentral areas which are involved in sensorimotor activities. Numerous studies have been published both before and since that time dealing with thalamic afferents to the sensorimotor cortex in the rat (94, 461), rabbit (173, 376, 411) and primates, including man (14, 90, 93, 103–105, 364, 393, 453–455). It is now well-established that the precentral areas 4 and 6 receive fibers from the ventrolateral nuclear groups of the thalamus (cf. 90, 378, 418, 457) which increase in size at higher levels in the phyletic scale concurrently with the increased size of cerebellar hemispheres in higher mammals (393). The number of fibers reaching area 6 from the thalamus increases rapidly in higher primates (cf. 458). Certain topographic patterns of distribution in areas 4 and 6 have been described for these fibers in relation to the position of their cell bodies in the thalamic nuclei (cf. 90, 455, 458). Thalamocortical connections to parietal areas 5 and 7 originate from the nucleus lateralis posterior of the thalamus (90, 96, 353).

In the rat, an overlap exists between the excitable cortex and the cortical area receiving projection fibers from thalamic nuclei relaying sensory information (186, 252). The problem of the existence of sensory projections to the precentral cortex of primates must also be considered (104, 105, 136; cf. 458); it is discussed in Chapter XVII by Rose & Mountcastle in this work. There is no general agreement that cutaneous sensibilities are confined to the postcentral gyrus, as has been suggested (290, 478), since potentials have been recorded in the precentral cortex from stimulation of either muscular or cutaneous nerves after postcental ablation (287, 387). Stimulation of dorsal roots was already known to produce responses in the motor cortex (476), but they had been tentatively interpreted as carrying proprioceptive information (474). In man, sensations persist on stimulation of the precentral gyrus after postcentral resection (357, 358) and frequently involve a 'desire to move.'

The mapping in the cortex of responses from deep somatic stimulation has given conflicting results. Some authors consider that kinesthetic sensibility is exclusively represented in the postcentral gyrus and is based on proprioceptive afferents from joint and fascial receptors rather than from muscular afferents (337, 338). According to other authors, deep sensibility may be largely represented in precentral motor cortex (5, 8). Overlapping representations of widely separated peripheral points were found, with the same basic arrangement of major body parts, similar to that seen in the tactile representation (5). The proprioceptive nature of impulses capable of evoking responses in the somatosensory cortex of the cat (54, 313) has also been demonstrated (21). Responses evoked in the motor cortex by stimulation of muscle nerves are not abolished by removal of the cerebellum (387).

A progressive corticalization of the function of weight discrimination has been observed (383, 385, 386). The elaboration of this type of perception, which would seem to require the participation of proprioceptive sensibilities, involves the cortex of the parietal lobe. Damage to any portion of the parietal

cortex results in a small but definite impairment in this function in man. However, the essential participation of motor mechanisms cannot be excluded by these studies. It would appear that any motor deficit would interfere with the performance of the essential observations necessary to such an anaylsis.

Efferent fibers from the cortex duplicate the thalamocortical ones in many areas and terminate largely, but not exclusively, in the same thalamic nuclei (364, 447; cf. 240, 353). Physiological data (125, 133, 342, 346), as well as recent anatomical studies concerning areas 4 and 6 (240) and the parietal lobe (cf. 239, 353), are available. Numerous investigators have advanced hypotheses concerning the functional role of these fibers, called by Ramón y Cajal (371) 'de l'attention expectante.' Reference should be made to the work of Peele (353) in which these ideas are reviewed. They tend to attribute to these fibers a role in the processes of attention by regulating inputs to the cortex. This problem will be discussed further below.

Striopallidothalamocortical Interrelationships

An important role in cortical motor regulation has been attributed (71, 72) to indirect afferents to the precentral motor cortex from the globus pallidus via the ventrolateral nuclei of the thalamus. Descending cortical influences to the pallidum may be direct or may pass through the caudate nucleus. These topics and the effects of interruption of certain corticosubcorticocortical circuits in the production of abnormal movement are discussed in Chapter XXXV by Jung & Hassler.

The pallidum is said to receive cerebellar afferents directly via the brachium conjunctivum (82) and indirectly via the red nucleus (78), in addition to the afferents from the putamen and caudate nucleus (cf. 306, 350, 372). The caudate nucleus in turn may be activated not only by cortical but also by thalamic afferents. Afferent fibers to the caudate nucleus from the so-called 'diffuse projection system' of the thalamus (discussed by Jasper in Chapter LIII of this work) have been described (102, 366), but their existence has been disputed (344). Anatomical and physiological data concerned with this problem have been reviewed (410) with evidence for the existence of thalamostriatal connections.

Changes in the electrical activity of thalamic nuclei and of the cerebral cortex have been observed during stimulation of the caudate nucleus (195, 412, 434), although some of these findings are still disputed (213). Since the existence of caudate-cortical connections is uncertain (309, 370, 412), it has been suggested (412, 434) that the changes in cortical activity from caudate stimulation take place via the pallidum and thalamic and subthalamic nuclei through pathways including the ansa lenticularis (cf. 306, 350, 372). These studies, however, do not shed any light on the essential problem of the role of the striatum in cortical motor mechanisms. Striatal effects are certainly capable of influencing 'motor' activities at lower levels of the central nervous system as indicated by the findings reviewed in Chapter XXXV by Jung & Hassler in which the functions of the basal ganglia, as gleaned from experiments of stimulation and lesions of different nuclei, are discussed.

Cerebellocerebral Interrelationships

For a complete account of cerebral and cerebellar interactions concerned with phasic and tonic muscular activity, reference should be made to the chapters by Brookhart, French, Jung & Hassler and Eldred in this work.[3]

No specific role can as yet be assigned to the cerebellothalamic (82, 83, 104, 105) and rubrothalamic (78, 447) streams of afferent volleys which relay in the cerebellar nuclei and pass to the cortex via the ventrolateral nucleus of the thalamus (cf. 457). Facilitatory (331, 332, 380) and inhibitory (332, 333) influences on cortically-evoked muscular activities have been disclosed by stimulation of neocerebellar and paleocerebellar cortex (see Chapter LI by Brookhart in this work), but it has not yet been established whether these actions are mediated through the pathways outlined above, or whether they occur exclusively through spinal mechanisms (334). Some of the evidence, however, would suggest that the cortex is the place at which facilitation, at least, can occur (334). An increase in the electrical activity of the motor cortex has been described during stimulation of the neocerebellum (456), but interpretation of these data seems difficult. In fact, stimulation of the nucleus ventralis lateralis produces varying effects on the activity of different neurons in the motor cortex (267, 268). Pyramidal cells which send their axons into the pyramidal tract may be excited. However, their activity may be reduced by reason of lessened excitation from cortical interneurons. The firing of these interneurons is indeed abolished by stimulation

[3] A comprehensive study has been published by Dow & Moruzzi (121a).

of the nucleus ventralis lateralis through an action which has been interpreted as inhibitory in nature. On the other hand, inhibition of cortically-induced movements has been reported from simultaneous stimulation of the motor cortex and the nucleus ventralis lateralis (26). This action, however, is not mediated at the cortical level.

The evidence cited concerning the behavior of cortical units following stimulation of the nucleus ventralis lateralis thalami may support the hypothesis of the coexistence at the cortical level of a damping cerebellar influence as well as an independent effect of a facilitatory nature. The same paleocerebellar stimulation produces opposite effects on motor responses depending on the background of activity artificially induced in the motor cortex as with strychnine (332). There remains the basic difficulty of ascribing these influences to actions exerted partially, at least, at the cortical level.

The question as to whether cerebellar impulses reaching the cortex after relaying in the thalamus may convey some particular sensory attribute is in no way solved by the experiments discussed above. Since weight discrimination is permanently lost in the monkey only if, in addition to the medial leminiscus, the dentatorubrothalamic tract is also interrupted, whereas section of either alone does not produce permanent deficit (398), it might be inferred that these impulses may carry information of a precise sensory modality. Yet, cerebellar influences seem capable of modifying evoked potentials in the sensory cortex which probably provide the background for an appropriate motor behavior. It has been found that acoustic (406), as well as somatosensory and visual (Snider & Sato, personal communication) evoked potentials in the cortex, are greatly modified by a preceding cerebellar volley.

The cerebellocerebral connections are paralleled by the corticopontocerebellar paths (see 219; Chapter LI by Brookhart). Just as cerebellocerebral paths are not limited in their projections to motor areas but involve sensory cortex as well, so also descending pontocerebellar paths arise widely in the cortex outside the motor areas. The functional role of these very powerful streams remains largely unknown. It has been suggested that those which arise from the parietal lobe, at least, may be involved in the regulation of sensory inputs (354); but in the absence of experimental evidence, other hypotheses cannot be discarded. Thus, Ruch (384) considers that the role of the cerebellum in movement is to compare the action initiated at the cortical level with the image of the resulting motor performance transmitted to the cerebellum for the periphery. From this comparison, the cerebellum would initiate appropriate corrections to minimize discrepancies.

The experiments of Fulton and his colleagues (24, 163) bear directly on the problem of reciprocal cerebral-cerebellar interconnections in relation to movement. The tremor of decerebellated cats was abolished by decortication, and in the baboon and macaque by resection of areas 4 and 6. The ablation of area 6 alone increased the tremor. If the fact that voluntary movements are reduced in range and quality by cortical resection alone is neglected, the tremor, which is related to 'voluntary' movements, and which can be taken as a sign of disorganized function, is abolished by suppressing this function. Even if there is no doubt that the corticocerebellar interrelationships provide the basis of an exceedingly important regulatory system (405), the problem seems, however, to be of a greater complexity. Combined cerebellar and corticomotor ablations produce greater deficits than would be expected from summation of the effects of the two ablations performed separately, according to the observations of Luciani (280) confirmed by Carrea & Mettler (81). In addition, the importance of other systems has also been suggested by the finding that lesions of the contralateral ansa lenticularis greatly reduce the cerebellar tremor and ataxia following cerebellar cortical and nuclear lesions (79). These disturbances have been tentatively interpreted as at least partially due to intact outflows from the globus pallidus.

Intra- and Interareal Connections of Ipsilateral Hemisphere

The functional role of intrahemispheric connections is far from clear. This problem is not exclusively confined to the so-called intercortical and intracortical association fibers. It is also a matter of the size of the cortical field and the nature of the influences which may be exerted both by the numerous recurrent axon collaterals of cortical cells and by the horizontal cells in the first layer (371). Relevant to the same problem are also the questions of the receptive field of the individual cortical neuron, as may be indicated by the size of its dendritic arborization, and the extent of the field of distribution of each afferent fiber to a number of adjacent neurons (cf. 396). Studies relevant to these problems in normal and isolated cortex are discussed in the recent book by Burns (74).

We will consider here only intracortical and intercortical connections. Studies with local strychninization (131, 295) have brought only limited knowledge. Significant difficulties beset this method (99, 155, 299). Only the anatomical investigations appear to fulfill the essential criteria of accuracy, but even here discrepancies arise.

Area 4 is extensively connected within itself (cf. 240, 321–324) and also receives abundant fibers from postcentral areas 1, 2 and 3 (240, 307, 321–324, 353), as well as from area 5 and 7 (cf. 353). The supplementary motor area also sends fibers to area 4 (121). Connections seem to exist between the paracentral lobule and the cingulate cortex (240). In turn, area 4 projects to area 6 and to more rostral regions (cf. 321–324) as well as to the parietal convolutions 5 and 7 (353). Numerous association fibers go to the postcentral gyrus (298; cf. 240, 321–324) and form with those running in the opposite direction a large U-shaped bundle (438, 440). In addition to intra-areal connections (240), area 6 receives fibers from area 4 and also from temporal (302, 468) and parietal areas (314, 353). Other connections to area 6 have been described with strychninography (468). Area 6 sends fibers to the postcentral and parietal areas (321–324) as well as to area 4 (240, 307).

There are extensive connections within the parietal areas including those between 1, 2, 3, 5 and 7, with area 3 sending fibers to area 5, and areas 1 and 2 to area 7 (301, 314, 321–324, 353). In turn, area 5 projects to area 2 to a greater extent than to areas 3 and 1. Areas 5 and 7 are abundantly interconnected, and area 7 sends fibers to 1 and 2. Fibers from parietal areas have been described as reaching the superior temporal gyrus and the occipital lobe (353). Histological and strychninography studies, giving a more detailed description of the connections of precentral and postcentral areas and their subdivisions, may be consulted (36, 37, 135, 238, 239, 294, 295, 300, 415).

Callosal Interhemispheric Connections

Precentral and postcentral motor and sensory cortex receive through the corpus callosum numerous fibers from the cortex of the opposite hemisphere. This commissure, mainly concerned in cortical interhemispheric connections, is seen only in placental mammals and not in the monotremes or marsupials. In the latter, however, motor and sensory cortical areas are closely interconnected through the unusually large anterior commissure (Adey, W. R., unpublished observations).

Most authors agree that callosal fibers arise from small and medium-sized pyramidal cells, the majority of which are located in the fifth and sixth layers. Callosal fibers terminate in fine filaments in the superficial layers of the cortex, mostly superficial to layer 4 (cf. 58 for references). The existence (435–436) of an increased number of terminal arborizations at the cortical level at which the large pyramidal neurons are located is disputed (86), but physiologically there is clear evidence that callosal volleys will activate neurons which send their axons into the pyramidal tract (175). (See also Chapter XXXIV by Patton & Amassian in this work.) Electrical stimulation (87, 107, 108, 260, 352; cf. 55, 58) or strychninization (34, 167, 181; cf. 55, 58) of restricted points on the cortex of one hemisphere results in contralateral cortical responses which are usually maximal in the homotopic point but may also be distributed in a heterotopic fashion. These investigations show inequalities in the density of callosal connections between homologous areas. In the Rolandic motor area, face, neck and trunk subdivisions have a dense callosal interconnection (34, 108, 167). These areas are involved in motor functions usually requiring synergism between the two sides of the body. These findings contrast sharply with the arrangement in leg and arm areas where no callosal fibers are present. While these data are in agreement with anatomical observations (239, 240), in other aspects discrepancies exist. Histological data may be regarded as more reliable. Numerous callosal fibers were found by Minkowski (321–324) and confirmed by Milch (314) and Peele (353) interconnecting the pre- and postcentral gyri of the two hemispheres but have not been seen by Krieg (240). Extensive connections between area 6 in the two hemispheres have been described (240, 307). In the human brain many callosal fibers emanate from area 6 (319). Connections between area 5 and contralateral areas 5, 3, 1 and 2 have been described, and also a few with 4 (239, 314, 353). Peele (353) has observed projections from area 7 to contralateral areas 7, 5, 2 and 1 in decreasing order of significance.

The study of the functions of these callosal interconnections probably began in 1879 with Brown-Séquard (69). Bremer *et al.* (58) have reviewed the literature in this field. In 1939 Moruzzi demonstrated in the rabbit that subliminal stimulation of the cortical area from which masticatory movements can be obtained reduces the threshold of the homologous area of the opposite hemisphere to electrical stimulation (330). In the cat, a sustained facilitation of the

potential evoked in the acoustic area by a sensory volley has been observed as a consequence of callosal inputs (cf. 55). This phenomenon is found in the *encéphale isolé* cat but not in anesthetized animals (87). All synchronous volleys reaching a given sensory cortical area in one hemisphere produce a response in the homologous area of the opposite hemisphere, and the impulses responsible for this response have been shown to cross through callosal fibers (60).

Despite all the evidence indicating an important exchange of messages between the cortex of the two hemispheres through the corpus callosum, no information as to the function of these connections has been gleaned from transecting it surgically. In the cat, dog and monkey, no changes in the spontaneous behavior of the animal, nor deficits in sensory or motor functions, seem to occur as a result of section of the corpus callosum in the absence of intercurrent cortical damage (cf. 58 for references). This factor may well account for gross functional changes seen by early workers after callosal section, as discussed by Bremer *et al.* (58). Minor changes, as observed by other authors, following this procedure (234), resemble in many respects the effects of cingulate cortical resection as described by Kennard (233).

In man, agenesis of the corpus callosum is not characterized by any demonstrable deficits in the execution of movements or sensory perception (cf. 58 for references), although no substitution would seem possible for callosal functions. In primates, other interhemispheric commissures are not concerned in corticocortical relationships with the exception of certain portions of the anterior commissure (34, 296).

Surgical section of the corpus callosum in human subjects is rarely followed by any deficits, provided hemispheric lesions are absent (13). Since, however, a temporary motor dyspraxia can occur if motor or sensory deficits were present preoperatively, the hypothesis has been advanced that the corpus callosum can mediate a facilitating function in fine movements (402). The transient nature of these disturbances would not appear to be inconsistent with this hypothesis since compensation may occur on the basis of ipsilateral mechanisms. Indeed, it is clear that motor apraxia cannot be attributed to callosal lesions alone (cf. 58).

A complete and critical account of the anatomy, physiology and pathology of callosal functions has been provided by Bremer *et al.* (58). The transfer of memory traces between the two hemispheres through the corpus callosum is discussed in Chapter LXI of this work by Galambos & Morgan.

MAJOR EFFERENTS FROM CORTICAL AREAS CONCERNED IN SENSORIMOTOR INTEGRATION

Despite the difficulties which may attend attempts to categorize cortical efferent motor pathways, with the inevitable aspects of inadequacy entailed in rigid schemes of descending connections, the problem of these efferent pathways, depicted in figure 5, may be discussed from two major points of view. There is, first, the consideration of the cortical origin of fibers forming the pyramidal tract, with particular reference to the contributions to this tract from areas outside the precentral strip, and including regions of the parietal, temporal and occipital lobes. A corollary to such a study is the assessment of the extent of the distribution of fibers arising in the cortex and running at least part of their course through the internal capsule and basis pedunculi in company with corticospinal fibers but terminating in mesencephalic, pontine and medullary areas which form part of the reticular formation. These fibers may ultimately exercise a controlling influence on spinal motor centers through reticulospinal pathways.

The second category of cortical efferent pathways includes those fibers which form an 'extrapyramidal' system, and which run a subcortical course through the basal ganglia and diencephalic areas to reach the reticular zones of the brain stem. These pathways are presumed to be multisynaptic in many instances.

It is obvious that such a subdivision is in large measure artificial since the pyramidal tract has many fibers which terminate in brain-stem reticular areas and, thus, exercise their spinal influence through 'extrapyramidal' pathways (303). These profound extrapyramidal influences are fully described in Chapter XXXV by Jung & Hassler in this work, and attention will therefore be directed here primarily to the origins and supraspinal distribution of the pyramidal tracts. The long descending tracts in man have been extensively reviewed by Nathan & Smith (345) with a discussion of the earlier literature. Lassek (258) has summarized our knowledge of the pyramidal tract, and aspects of its termination have been reviewed by Bernhard (46). The pyramidal tract is the subject of Chapter XXXIV of this work by Patton & Amassian.

Cortical Origin of Fibers of Pyramidal Tract

In 1874 Betz (48) described the giant cells in the precentral gyrus which bear his name. Since, how-

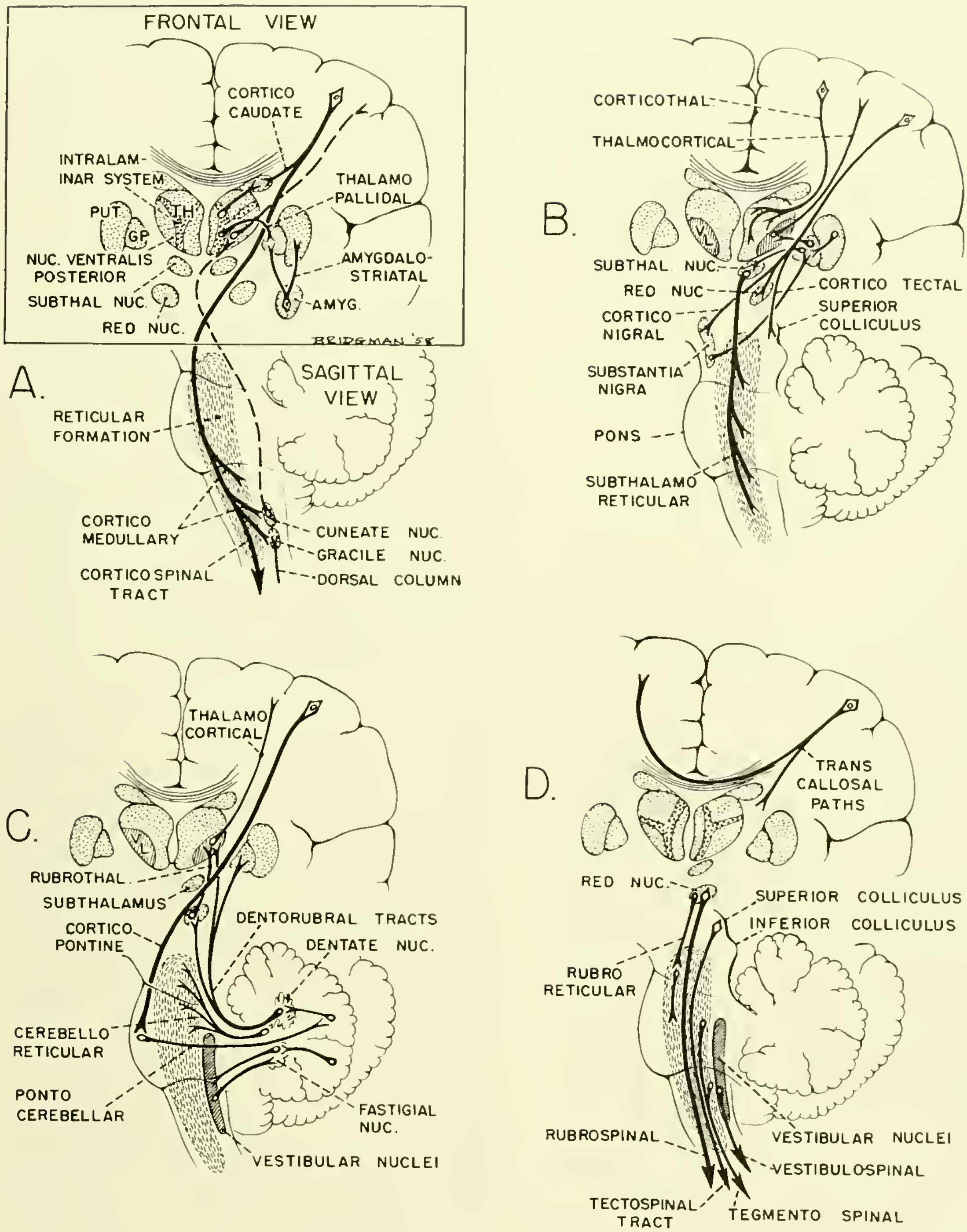

FIG. 5. A scheme of major corticosubcortical interrelations. In each figure the cerebral hemisphere has been drawn in coronal section and the brain stem in sagittal view. *A:* Arrangement of the primary sensory pathway (*dashed*) and the corticospinal, corticomedullary, corticostriatal and amygdalostriatal pathways. *B:* Major corticothalamic, corticorubral, corticonigral and rubroreticular connections. *C:* Corticopontocerebellar, cerebelloreticular, cerebellovestibular and cerebellorubrothalamic paths. *D:* Origin of the main subcortical motor influences descending to spinal levels.

ever, they number only 25,000 in each hemisphere, and since there are approximately one million fibers in the human pyramidal tract in the upper medulla, many of these fibers take origin in other cells. von Monakow (450) pointed out that these cells could not be the only source of pyramidal fibers since very few Betz cells occur in the main face and arm motor strips. This view was supported by Mettler's (304) finding that progressive impairment of movement, rather than progressive paralysis, follows removal of increasing portions of one hemisphere in the monkey.

EXTENT OF FRONTAL LOBE CONTRIBUTIONS TO PYRAMIDAL TRACT. On the basis of regeneration studies, Flechsig (146) concluded that the greater part of the pyramidal tract in man comes from the precentral gyrus. Degeneration is severe when the lesion involves the upper and middle thirds of this gyrus and the paracentral lobule; but after lesions affecting the lower third, the number of degenerating fibers in the pyramid is so small that usually a distinct area of degeneration cannot be found in the pyramids. Mettler (305) removed area 4 in the macaque and found that the myelinated fibers in the medullary pyramid were completely degenerated. Lassek (256) found in the macaque that extirpation of area 4 causes degeneration of one-third of the pyramidal fibers just rostral to the decussation and that these are the largest fibers.

The extent to which the premotor cortex, lying anterior to the precentral gyrus, contributes to the pyramidal tract is still debated. Bilateral excision of area 6 in a human patient with parkinsonism leads to degenerating axons in the pyramidal tract (319). Minkowski (321–324) traced degenerating fibers in the pyramidal tract of the macaque down to the lumbar segments, following lesions in that part of the frontal lobe lying immediately anterior to the precentral gyrus. Both Hoff (209) and Kennard (229) reported that in the monkey, fibers arising in area 6 could be traced in the pyramidal tract as far as the second sacral segment, and Kennard found that they were intermingled with those from area 4 at all levels of the tract. Both these workers found fibers from area 6 running bilaterally in the lateral pyramidal tract. Levin (264) and Levin & Bradford (265) criticized these findings on the basis that the degeneration observed by Kennard and Hoff arose from incidental damage to area 4. Verhaart & Kennard (433) subsequently repeated these experiments with more limited lesions in area 6 and noted a much reduced degree of degeneration in the pyramid. There is general agreement that in the monkey no region rostral to area 6 contributes to the pyramidal tract (229, 307).

Dejerine (114) concluded that the frontopontine bundle joined the corticospinal tract somewhere between the peduncle and the lower pons. This opinion was supported by Verhaart (432) from a study of two gibbons which indicated that some small fibers running with the frontopontine tract leave this tract in the pons and continue caudally with the corticospinal tract. However, Meyer *et al.* (310) and Beck (42) have found no evidence that Arnold's bundle, which is formed of fibers originating from granular frontal cortex, excluding area 8, sends significant numbers of fibers into the corticospinal tract.

CONTRIBUTION OF POSTCENTRAL CORTEX TO PYRAMIDAL TRACT. Mellus in 1894 removed a small part of the postcentral thumb area in the monkey and observed degenerating fibers bilaterally in the pyramidal tract (297). On the basis of both animal studies and human pathological material, von Monakow (450) concluded that a small part of the pyramidal tract arises in the parietal lobe. Extensive subcortical connections from areas 5 and 7 were seen by Clark & Boggon (96) and Mettler (301), including fibers running into the peduncle, pons and pretectal region, and into or through the nucleus ventralis posterolateralis, in a monkey which also had some injury to areas 18 and 19. Biemond (49), Sakuma (389) and Uesugi (429) described similar projections in the macaque, including ipsilateral and contralateral projections into the pyramidal tracts. Sunderland (416) traced a large parietal component through the lateral half of the cerebral peduncle into the pontine gray where most of the fibers terminated but some entered the medullary pyramid.

Peele (353) has provided an extensive review of the parietal contributions to the pyramidal tract in the monkey. In addition to a parietospinal component, all parietal areas send fibers to the thalamic nuclei, including ventralis posterolateralis and medialis. Fibers from rostral parietal areas terminate rostrally in the nuclei. All parietal areas send fibers to pontine nuclei of the same side, and all areas send fibers through the pyramid to the spinal cord. In the cord these fibers run in the lateral pyramidal tracts of both sides, the majority running contralaterally. Peele concluded that the parietospinal fibers arise from cells located in the external and internal pyramidal laminae, whereas parietothalamic fibers arise

in the fusiform layer. In Peele's view, this parietal projection system may form a mechanism for sensitization of sensory neurons. Confirmatory evidence of the existence of parietospinal projections in the monkey comes from the finding of Levin & Bradford (265) that degeneration of cells in areas 3, 1, 2 and 5 follows hemisection of the cord at the fourth cervical segment.

By contrast with these findings in the primate, Chambers & Liu (85) found no evidence in the cat for an origin of the pyramidal tract from parietal areas, nor from occipital and temporal areas. They concluded that it arises only in the sigmoid, coronal and anterior ectosylvian gyri.

EVIDENCE CONCERNING PYRAMIDAL TRACT FIBERS ARISING IN TEMPORAL AND OCCIPITAL LOBES. Approximately one-third of the fibers of the pyramidal tract remain after complete frontal lobotomy in the monkey. All are fine fibers and all are of cortical origin (257). Many of the remainder may take origin in the parietal lobe, but some at least may arise in temporal and occipital areas. Evidence for a temporal and occipital origin for these fibers is scanty. Walberg & Brodal (452), using the Glees method of silver impregnation in the cat, have traced degenerating fibers via the internal capsule, cerebral peduncle, longitudinal bundles of the pons and medullary pyramid to the lumbar level of the cord. Some of these fibers passed via the corpus callosum to the contralateral internal capsule to descend in the contralateral cerebral peduncle and pyramid. Many of these fibers crossed in the pyramidal decussation to descend in the opposite lateral corticospinal tract, but the ipsilateral lateral corticospinal tract and both ventral corticospinal tracts all showed degenerating fibers.

While the precise extent to which cortical regions outside the precentral motor area contribute to the pyramidal tract appears to vary in different species, and confirmatory evidence is required concerning the contributions from such regions as the temporal and occipital lobes, there is no evidence that any of the fibers of the tract have a subcortical origin (257, 265).

Descending Connections of Pyramidal System

While the spinal connections of the pyramidal tract are described in detail in Chapter XXXIV by Patton & Amassian in this work, attention may be directed here to those pyramidal connections which may be particularly concerned in sensorimotor integration.

EFFECTS OF STIMULATION AND SECTION OF CEREBRAL PEDUNCLE. Section of the peduncle has attracted attention as a means of relieving involuntary movement (cf. 259). Stimulation with a 60 cycle sine wave current gives rise to movement in the human only from the intermediate portions of the peduncle, with movements of the lower limb evoked from more lateral zones than for the upper limb. Section of the peduncle to a depth of 7 mm (probably involving the substantia nigra) in the lateral half to four-fifths produced only a transient weakness disappearing in a few months in many cases. The relatively small amount of paresis seen from such a section may be due to the cut not involving the anticipated portions of the peduncle by reason of the small size of the peduncle in these cases or by the displacement of an abnormal peduncle. Where excitation rostral to the cut was continued during sectioning until movements were practically abolished, the ensuing hemiparesis was then usually moderate and long-lasting (cf. 259). It is suggested from these results that damage to these fibers at their cortical origin gives rise to much more severe and lasting paresis than interruption of the fibers at any other point in their course. This may be explained in terms of 'pyramidal' and 'extrapyramidal' cells in the cortex being capable of excitation of spinal motor units via other pathways. The lack of paresis seen here following lesions of the pyramidal tract does not support the notion of a precise somatotopic cortical representation. There is some evidence of somatotopic localization in the internal capsule, cerebral peduncle and pons of the monkey and rat, but the overlap is considerable and increases from above downwards (39).

In similar studies of the effect of section of the basis pedunculi in monkeys (76), the paralysis was intermediate between a spastic and a hypotonic paresis, and was characterized by a hypotonicity of all muscle groups excepting the extensors of the digits, by hyperactive deep reflexes and by absence of clonus. It is assumed from these results that inhibitory pathways descending from the cerebral cortex do not course exclusively within the basis pedunculi. The majority of the fibers, the interruption of which leads to hypertonicity, and also those mediating clonus would appear to have deviated from the corticospinal projection prior to reaching the cerebral peduncle. Those, the interruption of which leads to hyperreflexia, accompany the corticospinal projection

through the cerebral peduncle but deviate before reaching the pyramids.

EFFECT OF SECTION OF MEDULLARY PYRAMID. Section of the medullary pyramid of monkeys and chimpanzees is followed by a flaccid paralysis, and the muscles show conspicuous atrophy from disuse (289, 422, 423). Tower (422, 423) has interpreted these results as attributable to a deficient function, rather than to a release phenomenon, and concludes that there is no evidence of an inhibitory action by the pyramidal system. Walshe (463) does not accept this conclusion, contending that the prominent Babinski response following pyramidal section in the chimpanzee should be regarded as a release phenomenon. Denny-Brown (117) characterizes Tower's findings on pyramidal section as "the final blow to the clinical conception of disorder of the pyramidal system," but Walshe considers this premature.

TERMINATION OF PYRAMIDAL TRACT FIBERS IN MEDULLA. It has long been known that the fiber content of the pyramid at the lower end of the medulla is significantly less than at the upper end. Some of these fibers may end in relation to neurons of the reticular systems of the central zones of the medulla, but there is evidence that many terminate more dorsally among the neurons of sensory nuclei and may, thus, participate more directly in modulating the sensory influx essential to motor mechanisms (85, 243). These investigations have indicated that following various lesions in the cat, including hemidecortication, frontal decortication and selective lesions of either leg, arm or face areas of the motor cortex, degenerating recurrent as well as transtegmental fibers can be traced from the pyramidal tract to the region along the ventral aspect and into the hilus of the cuneate and gracile nuclei. Other fibers can be traced to the medial part of the spinal trigeminal nucleus and adjoining lateral parts of the tegmentum. This cortical projection to the rostral part of the spinal trigeminal nucleus and its vicinity originates mainly in the face area, whereas the projections to the cuneate and gracile nuclei have their main origin in the fore-limbs and hind-limbs areas, respectively.

The question of the presence of ascending fibers in the pyramid requires confirmation (cf. Chapter XXXIV by Patton & Amassian in this work), but suggestive evidence has been obtained in the cat by Brodal & Walberg (62) who concluded that they arise in the spinal cord and also in the cuneate and gracile nuclei. Nathan & Smith (345) have described ascending fibers in the pyramid after lateral spinal tractotomy in man, and these fibers were traced through the pyramidal decussation into the pons, cerebral peduncle and internal capsule. Physiological evidence concerning ascending fibers in the pyramid is inconclusive.

EFFECTS OF CEREBRAL LESIONS IN INFANCY ON RESIDUAL PYRAMIDAL FUNCTIONS. Ipsilateral control in infantile hemiplegics is often associated with hypertrophy of the ipsilateral pyramidal tract. von Monakow (447) described a compensatory hypertrophy of one corticospinal tract following degeneration of the other in infancy. Reports of similar findings may be seen in the older literature (84, 115, 286). This hypertrophy of the remaining pyramid may double its volume and is then associated with a large uncrossed lateral and ventral corticospinal tract from the healthy hemisphere. Verhaart (432) believes that this is not due to an increased number of fibers but simply to an abnormal number of thick fibers with a diameter greater than 3 μ, whereas the number of smaller fibers is within normal limits.

SENSORIMOTOR INTEGRATION IN PERFORMANCE OF MOTOR ACTIVITIES

Reflex activation of pyramidal neurons by impulses reaching the cortex along afferent pathways has been seen in a variety of experimental conditions. Stimulation of relay or diffusely projecting thalamic relay nuclei (23, 65, 351), as well as peripheral somatic (12, 25), visual (25, 460) and acoustic (25) stimulation, has been shown to induce changes in the excitability of the motor area, or to produce a discharge in the pyramidal tract. Amantea (19, 20) found that following strychninization of the motor representation of one limb, stimulation of the skin of the same limb intensified the clonus produced by the strychnine until ultimately a generalized seizure might follow. A seizure can also be induced by strychninization of cortical sensory projection areas and stimulation of the corresponding receptor organs, as shown by Clementi for the visual (98) and acoustic (97) areas. The cortical origin of the motor activities in both Amantea's and Clementi's experiments is proved by the fact that ablation of the motor cortex prevents the appearance of the epileptic attack (50, 159). An electrophysiological analysis of Clementi's photic epilepsy (417) has led to the conclusion that interareal connections are involved in the spread to the motor

cortex of the convulsive activity without, however, excluding the probable participation of subcortical structures (cf. 335), as occurs in photic epilepsy induced with pentylenetetrazol (170).

Somatosensory (5, 8, 287, 387) and also visual and auditory (142) responses, often with characteristics different from those recorded in the respective areas of specific projections, have been observed in records from the motor area (cf. 15, 55). The data referring to the activity of single units within the motor and somatosensory cortex have been presented in Chapter XVII by Rose & Mountcastle and in Chapter XXXIV by Patton & Amassian in this work. We shall, therefore, confine ourselves to a few aspects of this problem. Li (personal communication) has observed that the firing of pyramidal neurons within the motor area may be influenced in various degrees by sensory volleys initiated in skin nerves. Activation of these pyramidal neurons can sometimes occur as a consequence of the synchronous sensory volley. Moreover, cortical stimulation may produce a sustained depolarization of pyramidal neurons, as shown in the intracellular records of Phillips (361–362). This observation may indicate that the excitability of these neurons is largely determined by a background synaptic impingement from other cortical cells. Many of the units studied by Li within the motor cortex, which could not be classified as pyramidal neurons on the basis of antidromic stimulation of the pyramidal tract, have shown either an increase or a decrease of their previous activity as a consequence of the sensory volley.

From these observations it may be concluded that sensory afferents initiate within the sensorimotor cortex changes in unit activity which in turn may influence the motor output. However, no reconstruction of the processes of integration on the basis of studies of single unit discharges is as yet possible. Also relevant to this problem is the question of the influences exerted by recurrent axon collaterals of the pyramidal neurons on adjoining cortical cells. The data presented in Chapter XXXIV by Patton & Amassian and new findings by Phillips (363) seem to indicate that the activity of the axon collaterals may not result exclusively in either excitatory or inhibitory processes.

Turning now to the role of deep somatic sensibilities in the regulation of motor acts, it has been demonstrated that alteration in the tension of the muscle may influence the movement elicited by stimulation of the motor cortex (171, 172, 469). Although these effects, due to the action exerted by proprioceptive and kinesthetic inputs, certainly occur mostly through spinal mechanisms as in the case of scratch reflex (428), section of the dorsal roots seems to deprive higher centers of a component necessary to their normal activity (336). It appears that the animal fails to use the deafferented limb, despite the retention of motor capacity, except in stereotyped and instinctive behavior, such as is seen in defensive acts (336). Older evidence suggests that the threshold of the motor area to direct stimulation becomes higher following this operation (336). Further observations support the view that the pyramidal tract rises in neurons which are not normally autonomous in the initiation of motor activity but are dependent on afferent volleys from the periphery in attaining their usual levels of excitability. Walshe (464, 465) has summarized the view that it is the afferent system, through its different receptors, which is concerned in this aspect of cortical integration (cf. 259).

The question of the representation of deep somatic sensibilities in the motor cortex has been previously discussed. No answers are yet available to numerous problems in this field. A puzzling observation is that section of the U-shaped bundle, between the precentral and postcentral gyri (357), or isolation of the motor cortex (251, 355, 451) is without consequence on motor performance. If the kinesthetic sensibilities, as elaborated in the cortex, play a role in the regulation of motor mechanisms, the further possibility must be considered that they play their part at subcortical levels, or that somatosensory inputs are available at the motor cortex, either directly or indirectly. There is disagreement about this second possibility (see page 814), due in part to the singular difficulties in the verification of hypotheses about the way kinesthetic sensibilities might influence patterns of motor activity at the cortical level.

The special senses, including visual and auditory, may likewise participate in the patterning of central activities related to motor functions. It is commonly held that acoustic stimuli are responsible for various forms of orienting reflexes which may involve not only the musculature of the ear, such as may be seen in certain instances in lower animals, but may also involve most of the body. It would seem, however, that while in these cases most of the movement is of subcortical origin, cortical participation is required when acoustic information is the only source of afferent inputs on which motor activity might be based in a sequence of skilled, purposive movements.

Visual inputs usually participate to a great degree in the regulation of motor performance. The rich-

ness and complexity of the processes involved here are well illustrated by the clinical observation that cerebellar ataxia in man can be overcome, to a great extent, by visual control of the movement. Even if it is impossible to determine where the integrative processes involved in this control take place, it is highly significant that no other inputs can reduce the ataxia consequent to lesions of the dorsal roots. While in the latter case the disorganization of motor control can be largely explained on a reflex basis, due to loss of proprioceptive afferent volleys in spinal centers, the role of visual inputs in overcoming cerebellar ataxia implies the intervention of more complex central processes in which higher functions participate. Attention by the subject to the motor performance is certainly one of these processes, and here neurophysiological techniques have recently provided certain basic correlates.

It has been postulated that modulation of sensory inputs by central activity is a process strictly bound to the mechanism of attention (cf. 279). Anatomical observations have shown that collaterals of pyramidal fibers terminate in the cuneate, gracile and trigeminal nuclei (85, 243). Physiological data on the role of these connections are not yet available, but it would seem reasonable to assume that somatosensory inputs may be modified, at the level of these relay nuclei, by the activity of pyramidal neurons. The anatomical observations quoted suggest mechanisms and pathways through which stimulation of the reticular formation may induce changes in the output of these nuclei (193). The possibility that the motor cortex, itself, can modify sensory inputs directly would appear to parallel the actions tentatively attributed to other systems of corticifugal fibers arising in sensory areas. Suggestions by earlier investigators in this area have already been mentioned. The question has been reviewed by Galambos (164) in relation to the problem of central control of acoustic inputs. Various sensory inputs other than somatic have also been shown to be susceptible to reticular stimulation. These results are reviewed in Chapter LII by French, in Chapter XXXI by Livingston and in the monograph by Rossi & Zanchetti (381).

Reverting to more strictly cortical aspects of sensorimotor integration, the overlap between the second sensory area and the motor representation in primates would appear to indicate a close relationship between sensory and motor activities in this cortical region, but this problem deserves further study. Experimental evidence concerning the possibility of evoking movements from both primary and second sensory areas has been reviewed by Hess *et al.* (197) who reported contralateral movements evoked in the cat by stimulation of the primary sensory area and homolateral movements from the second sensory area. The role of polysensory areas in relation to motor activity is unknown. Points have been mapped on the lateral surface of the cortex of the cat which respond to a variety of sensory inputs (cf. 15). A region has been found overlapping the representation of vestibular cortical afferents where interaction of acoustic and somesthetic inputs occur (57, 312). It has been suggested that this polysensory area may participate in integration of postural and purposive motor activity (57), but as yet no supporting evidence is available.

Vestibular inputs certainly participate in the regulation of posture and in the patterning of activity on which a motor act is based. While these actions are mostly subcortical (cf. 228), involving particularly cerebellar, brain-stem and spinal mechanisms, the vestibular projections to the cortex (see Chapter XXII by Gernandt in this work), as well as interaction of vestibular with other sensory inputs in the basal ganglia (392), suggest a contribution of these inputs to the cortical regulation of motor functions. Disorders of equilibrium are commonly seen clinically where lesions are localized in the frontal and parietal lobes, but it would seem that these functions have a greater and more direct influence on parietal lobe activities (cf. 113), possibly in connection to the formulation of the so-called 'body scheme' (cf. 113, 292). Equilibratory sensations were also produced by stimulation of the temporal cortex (358).

Role of Pyramidal System in Relation to Willed Movement

Voluntary movement is the subject of Chapter LXVII by Paillard in this work. The present discussion considers only a few aspects of this problem. The absence of adequate knowledge, which we have frequently emphasized in the course of this review, heavily besets the possibility of evaluating cortical components in the initiation of a voluntary motor act. It would appear even more difficult to attribute specific patterns of neuronal activity to such an act since learned movements are essentially adaptive and do not depend on the use of a particular group of muscles (218, 253, 254). This fact would seem to refute the hypothesis of a simple and unique pattern of neuronal activity in a given motor performance when this is considered as a means to achieve a goal.

This point of view offers at least a less discouraging approach to the findings that isolation of the motor cortex, or the infliction of a series of perpendicular incisions in it (251, 357, 409, 451), do not produce significant impairment of function. Furthermore, it has already been stressed that plasticity is one of the major attributes of the central nervous system, as indicated by functional recovery following extensive lesions. This factor of plasticity, which may be regarded as simply another aspect of the multiplicity of patterns mentioned above, may account for the changes which must occur in central processes in order to bypass both central and peripheral defects. Rearrangement of central control of motor processes would in fact seem possible, at least partially, particularly in certain instances in higher primates, in circumstances where the peripheral effector apparatus has been altered, as by a muscle transplant (cf. 408).

In addition to the effect seen in the quoted cases of experimental interference, it has been shown that the electromyographic responses recorded from muscles not directly involved in a given voluntary movement (111) are reduced with age (112), probably as a result of a more effective and economical pattern of central activity.

No data seem to be available to support concepts of the role of individual neurons in relation to the total motor output (202). In addition, the meager results of cytoarchitectonic studies in the interpretation of functions of different cortical areas strongly emphasize the difficulties of correlating structure and function in relation to integrative processes. As Golgi (179) so succinctly remarked many years ago, the specificity of function of different cortical zones depends not on the organization of these zones themselves, as revealed by cytoarchitectonic studies, but on the specificity of fibers entering and leaving these regions.

Such factors as attention, learning, memory and emotion are processes which, although poorly understood, certainly play an important role in the performance of both stereotyped and novel motor activity. It is, therefore, not surprising that knowledge concerning the problem of willed movement is still very meager. It must be recognized that none of the neurophysiological data presented here can account for the initiation and arrest of movement nor for the purposive changes made in the course of a movement on the basis of previous experience. It has been suggested that actions such as the sudden starting or stopping of motor activities, which may be regarded as at least one aspect of will, take place via pyramidal fibers arising in the primary motor area (423). This view agrees with the observation that a loss of many aspects of skilled movements follows ablation of cortical motor areas, implying the participation of the cortex in at least the initiation of these finely patterned aspects of motor activity. As Penfield (355) has pointed out, it is clear that the nature of voluntary action is determined according to sensory information. When, for example, one considers the extraordinary dexterity of hand movements, it is obvious that, in the full utilization of the precentral cortex, the nerve impulses which reach it must come in a pattern which is vastly varied in time of arrival, in rhythm and in the combination of ganglion cells selected for activation. Penfield concludes that the nature of voluntary action is determined in accordance with the guidance of memory and the conclusions of reason, and that complex integration must occur before the appropriate motor impulses arise in the precentral gyrus.

In Penfield's view, this volitional stream of impulses impinging on the precentral gyrus does not arise cortically since neither removal of the area anterior to the precentral gyrus nor ablation of the postcentral gyrus can entirely abolish skilled movements. Penfield looks to the centrencephalic system of the brain stem as initiating a stream of willed impulses capable of producing the action that is appropriate to all previously received information. It might be expected that this volitional stream of impulses must originate in ganglionic nuclei, such as the centrencephalic system, which have functional or preparatory connections with sensory and elaboration areas of both hemispheres. Walshe (463, 464) has also directed attention to the possible subcortical origin of these streams of controlling impulses, stating that "the human pyramidal system of itself initiates nothing, and to speak of it as responsible for this or that category of movements is to ignore the source and motive power of its activities."

Disorders of willed movements, such as occur in parkinsonism, in association with lesions of the basal ganglia and brain stem, have served to kindle new interest in the role of the corpus striatum in these functions. These studies have been reviewed by Clark (95), who points out that there are extensive connections between the intralaminar thalamic nuclei and the corpus striatum, and that the latter is in fact a highly important 'sensory ganglion', which receives by way of the intralaminar nuclei, patterns of afferent impulses mediated by the reticular system as a whole. Moreover, in birds the higher functional levels of

the sensory pathways appear to be represented entirely in the homologies of the intralaminar nuclei of the thalamus and the elaborate corpus striatum. So far as is known, the cerebral cortex of the avian brain receives no ascending pathways directly from the thalamus. Clark concludes that if the instinctive aspects of willed behavior are mediated at the higher functional levels of the brain by the intralaminar nuclei and the corpus striatum, it may be assumed that the equivalent system in mammals, and even in man himself, may perform comparable functions. Subtle changes in the ability to perform willed responses have been seen following striatal lesions in the monkey (4).

We have discussed here the problems of willed movements without specific reference to the brain-mind relationship. Little can be said at this stage concerning the functions of the mind in relation to the microcosm of the individual cell. Eccles (137) has accepted Sherrington's view that mind is not a form of energy and has developed hypotheses as to how nonenergy mind can act on matter at the cellular level, ascribing to certain minute 'influences' a capacity to act upon a synaptic junction and modify behavior. This point of view has been criticized by Lashley (255) on the grounds that the use of the uncertainty principle of Heisenberg in this connection is invalid and quite irrelevant to the question of causal determination.

An interesting and probably highly significant finding in relation to willed movements has been obtained by Kupalov. In a review by this author (242), an account is given of the establishment and elaboration of a shaking conditioned reflex in a dog. The conditioned response required much training with the dog assisting the initiation of the response by scratching the skin with the paw or rolling on the floor. In subsequent trials, the dog began to perform the movement to the conditioning stimulus with great alacrity. "In view of the way the dog shook, it seemed that movement was converted into a voluntary act."

Studies of Conditioned Motor Performance

The technique of conditioned reflexes has been applied in this field, first, to the study of sensorimotor interaction, and more recently with a view to providing, by a combination with electrophysiological techniques, a neurophysiological correlate of higher processes such as learning. These studies are considered in Chapter LXI by Galambos & Morgan in this work.

It has been demonstrated that conditioning photic stimuli may induce Clementi's photic epilepsy more readily than unconditioned stimuli of the same modality (293). The results obtained by Russian authors in this field demonstrate the occurrence of changes in electrical activity of both sensory and motor cortex during the establishment of an avoidance response, as summarized in a review by Rusinov & Rabinovich (388). Modification of the electrical activity in subcortical structures also occurred under these conditions. There remains, however, the fundamental difficulty of reaching conclusions from these data about the basic processes underlying the alterations in the recorded waves. The view expressed by some of the Russian authors in this area is too briefly reported in the review cited to permit comparison of their interpretation of the data with the knowledge of the mechanisms upon which neuronal firing appears to depend (138). It is unlikely that background activity, recorded with gross electrodes, reflects changes at the unit level, at least under most conditions.

Nevertheless, by the use of microelectrodes in conjunction with conditioning experiments, it has been possible to secure a more intimate view of integrative processes related to motor activity in different cortical areas. The pattern of firing of single neurons has been studied in the motor and sensory cortex of the monkey during the performance of a conditioned motor response in an avoidance situation. In the experiments of Jasper *et al.* (221) the units recorded within the arm area of the motor cortex, contralateral to the limb performing the avoidance act, have shown varied patterns of activity, as shown in figure 6. While acceleration of firing can precede and outlast the movement in some units, about a third of the units studied showed no change in firing patterns throughout this period. This occurred both for conditioned responses as well as during movement performed spontaneously by the animal. When the conditioning stimulus is present, the firing of other units can be arrested until the end of the conditioning signal. In still other units, a brief burst can appear at the onset of the conditioning stimulus without further participation of this unit in the response.

Under similar conditions, records from the sensory arm area have shown that the firing rate, which is usually increased, changes more commonly with

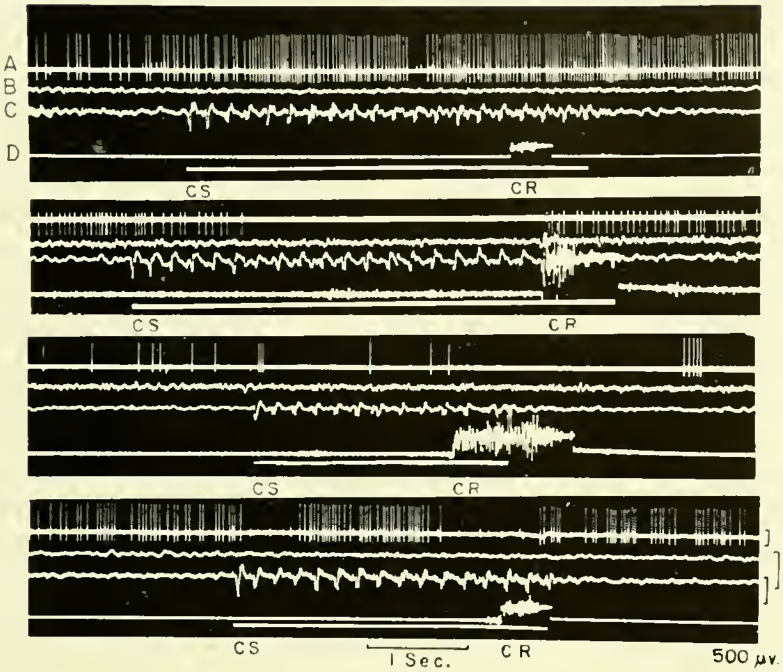

FIG. 6. Pattern of firing of units within the motor cortex during the performance of a conditioned avoidance movement. In each record *A*, microelectrode in the motor cortex; *B*, surface record from the motor area; *C*, surface record from occipital area; *D*, electromyogram from the arm performing the avoidance act (*CR*). This act involved the opening of a switch, indicated by an upward deflection in trace *D*, thereby interrupting a stimulating circuit which would otherwise have been activated following presentation of the conditioning stimulus (repetitive photic stimulation applied during the time indicated by the line at the bottom of the record). Four different patterns of unitary activity are shown. *Top to bottom:* acceleration of unit discharge preceding and outlasting the movement; arrest of unit discharge at commencement of conditioning stimulus, with return of discharge immediately following the CR; a brief burst of discharge at the onset of the CS with no further detectable participation of this unit in the response; and arrest of firing both on presentation of the CS and for some time before the performance of the CR, with return of discharge following the movement. No changes were observed in the pattern of firing of 25 to 30 per cent of units studied in the motor area containing the arm representation. [From Jasper *et al.* (221).]

movement itself as if it were the consequence of it. Changes in firing in anticipation of movement were infrequent and not important.

Parietal Lobe Influences on Motor Activity

The behavior of cells in the motor cortex, which show changes in firing rate before the movement, recalls the concept of the existence of a plan of anticipation as postulated by Liepman (272, 273). However, the difficulty here is in translating into neurophysiological mechanisms what is as yet only a psychological concept. Similar difficulties which also arise in the case of the body scheme do not, however, invalidate either of these concepts. There is much supporting evidence as to the role of the cortex in building up and continuously remodeling the image by which the subject is aware of his position in space and his postural attitude (cf. 113, 292). Certain types of agnosia and apraxia which follow lesions of the parietal lobe have led to localization in these regions of mechanisms involved in the formulation of the body image (cf. 113). As discussed by Shilder (395), this body scheme is based upon and built up through the sensory input but is subject to variations induced by emotional factors.

According to Denny-Brown & Chambers (119), the exploratory behavior of the monkey, in addition to its orientation in space, also depends mainly on an intact parietal cortex. Defects in behavior follow lesions in different areas of this cortex. Visual avoidance reactions in primates, including man, appear following posterior parietal ablation, while anterolateral ablations release similar reactions to tactile and nociceptive stimuli. Ablation of area 7 may bring about a more general release of all types of avoidance reactions.

Since parietal areas participate, on the one hand, in sensory functions by reason of afferent sensory volleys and also respond to stimulation by evoking movements, it is possible that in these areas at least a fairly strict correlation occurs between sensory input

and motor output. Polysensory projections have been described in the association cortex of cat brain (cf. 75), and the thalamic relays for these responses have been identified (51). Among others, the nucleus centrum medianum has been found to relay sensory information to regions in the anterior and posterior suprasylvian gyrus (17). This nucleus, a part of the so-called 'diffuse projection system' of the thalamus, also receives projections from many cortical areas and is the site of interaction of cortical descending influences and ascending somatosensory volleys (cf. 16). Furthermore, stimulation of this nucleus, in addition to producing widespread changes in electrical activity of the cortex, also produces changes in motor functions which take place through subcortical mechanisms (cf. Chapter LIII by Jasper in this work). This example of the centromedian nucleus is cited here merely to illustrate a particular aspect of the complex and involved corticosubcortical interrelationships which might play a very important role in sensorimotor integration. This conclusion is suggested also by the observation of reticular units which were found to be influenced by stimulation of the cerebellum and motor cortex, and by sensory inputs of different modalities (441, 442), as discussed in Chapters LII by French and XXXV by Jung & Hassler in this work.

Certain Corticosubcortical Interrelations in Motor Mechanisms

It has been suggested that the diffuse projection nuclei of the thalamus may play a role in the initiation of movements, in the processes of attention, or in both (220). The observation of motor disability and transient lethargy after thalamic lesions in the region of these nuclei (391) is not inconsistent with this hypothesis.

A greater body of information is available concerning the reciprocal relationships between the cortex and reticular formation which is discussed in Chapter LII by French in this work. While many questions concerning the mechanisms of cortical 'activation' by reticular action remain unsolved (cf. 381), it is, however, sure that the reticular formation can influence intracortical mechanisms by altering the probability of firing of cortical neurons, including those involved in sensorimotor activities (351, 473). Discharges recorded from single fibers in the pyramidal tract are altered as a result of cortical 'activation' by reticular action, concomitantly with the changes occurring in the cortical electrical activity (473). Evoked potentials in sensory projection areas are also modified as a result of arousal, following both natural sensory stimuli and reticular stimulation (cf. 59).

More work is needed before these actions can be defined in precise terms, but the overall picture of the electrical cortical activity in this condition of arousal is the one which can be expected in the course of integrative processes. This would seem to imply mainly a desychronized pattern of unitary activity necessitated by a temporal and spatial dispersion in which excitatory and inhibitory processes act through graded and algebraically summating actions (cf. 56). It would thus appear that reticular actions may affect in varying degrees sensorimotor cortical integration. The cortical efflux, in turn, is directed to a great extent to subcortical structures, including the reticular formation (cf. 156).

It has been suggested that subcortical facilitation of motor activity, as studied by means of prebulbar reticular stimulation on the monosynaptic reflex, is controlled at once, when initiated, by an inhibitory process which is cortical in origin since it can be abolished temporarily by cooling the cortical surface and permanently in the chronic decorticated cat. Hugelin & Bonvallet (213, 215, 216) describe these inhibitory cortical actions as originating from most of the cortex and mediated by 'extrapyramidal' fibers which, at the level of the pes pedunculi, enter the lateral hypothalamic area and reach the posterior diencephalic tegmentum. This cortical inhibitory action is tonic in character but increases slowly when subcortical facilitation is initiated. This produces, concomitantly with the action at the spinal level, a cortical 'activation.'

The quoted results resemble those obtained by Tower (421) who demonstrated that the stimulation of various cortical points, after section of the corticospinal tract, abolishes a background of muscular hypertonus and stops movements. Tower describes regional differences in the capacity of the cortex to produce these effects.

While many difficulties attach to specific interpretation of this (214) or other corticosubcortical interrelationships previously considered, their existence emphasizes the interdependence of ganglionic masses within the central nervous system when their activities are considered in relation to a behavioral act. In this respect the importance of the overlap between pyramidal and extrapyramidal functions in integrative processes necessary for a successful motor

performance probably expands beyond the purely mechanistic aspect of the problem to include some of the higher central processes, usually referred to as 'mental.' Knowledge of these processes is indispensable for the ultimate understanding of central activities underlying motor functions.

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The pyramidal tract: its excitation and functions[1]

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CHAPTER CONTENTS

ANATOMICAL FEATURES

THE PYRAMIDAL TRACT is primarily an anatomical rather than a physiological entity. Strictly defined, it comprises those neurons with descending axons[3] which traverse longitudinally the bulbar pyramids (fig. 1). Excluded are the thin strands of external arcuate fibers which stream transversely over the surface or, sometimes, through the substance of the pyramid (fig. 1); this exclusion is appropriate physiologically as well as anatomically. Inappropriately excluded by strict anatomical definition, however, are the corticofugal fibers which supply cranial motor nuclei. These fibers ('aberrant pyramidal bundles'), although presumably bearing the same functional relationship to cranial motor nuclei that the corticospinal fibers bear to spinal motor nuclei, depart from the main tract at the level of the pons and do not traverse the bulbar pyramid (110, p. 10). Inappropriately included are corticobulbar fibers which depart from the pyramid to terminate in the overlying reticular formation (95, 96), and hence are at least potentially pathways of the 'extrapyramidal' type. Thus, even at the bulbar level, where the tract is purest, it is both contaminated and incomplete. Figure 1 shows the relationship of the cat pyramid to other bulbar structures at the level of the inferior olive. The right pyramid is degenerated owing to ablation of the ipsilateral cortex one month previously. The histological change is evident, but the tract has lost little bulk, being about 1 mm thick; with a longer degeneration period, the pyramid shrinks grossly. The undegenerated fibers dorsal to the pyramid, and interposed between it and the olive, constitute the medial lemniscus. The proximity of the two tracts persists throughout the bulbar extent of the pyramid (41). The picture emphasizes the difficulty of either selective stimulation or selective section of the pyramid. Moreover, the proximity of the pyramid to such active structures as the lemniscus and the reticular formation (the entire dorsoventral extent of the bulb is only 4 to 5 mm), all immersed in an excellent conductor, indicates the necessity for careful depth measurements and differential recording in studies designed to measure electrical activity of the pyramids. With the exception of Lloyd's study (72) these pitfalls have rarely been taken fully into ac-

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[3] The question of ascending fibers in the pyramid is discussed below.

FIG. 1. Weil-stained section through medulla of cat surviving right hemidecortication for 1 month. Intact fibers between degenerated right pyramid and inferior olive constitute the medial lemniscus.

count, they have recently been re-emphasized by Patton & Amassian (82) and by Landau (54, 55).

Despite these reservations, the bulbar pyramid is the best level at which to study pyramidal tract function. At the suprabulbar and the cord level, and even in the decussation (80), the tract is hopelessly contaminated with other functional systems.

PYRAMIDAL DEFICIT; SECTION OF PYRAMID

The full extent of the bulbar pyramids can readily be exposed by reflecting the trachea and pharynx and removing the basiocciput. One or both pyramids can then be cut; care must be taken to avoid injury to the overlying basilar artery and its branches.[4]

The effects of experimental pyramidotomy have been studied in the rat (7), dog (92, 94), cat (50, 68, 75, 99, 100), monkey (89, 92, 101, 103), and chimpanzee (103). Unilateral lesions cause contralateral paresis, varying in severity according to the species. In rats, the flexor muscles are particularly affected, but the paresis diminishes, although it does not disappear, in 2 to 3 weeks. In cats and dogs, the hind limbs are more severely affected than the forelimbs. Walking is not permanently abolished, but there are striking disturbances in precise locomotory movements, e.g. walking a narrow track or ladder. The contact and visual placing reactions are diminished or abolished. The paretic limb exhibits decreased resistance to passive extension; resistance to passive flexion appears to be increased but may result from flexor hypotonicity (99).

In the monkey and the chimpanzee, the effects of pyramidotomy are more severe (103). The chief defect is the contralateral paresis involving the musculature from the neck down. This affliction is more severe in the chimpanzee than in the monkey; indeed, in the former the relatively stereotyped movements of progression appear to be somewhat impaired, although they are not abolished. In neither animal is paralysis ever so grave that the affected limbs are useless, but there is severe poverty of movement and loss of such fine movements as apposition of thumb and index finger in grooming or manipulating small objects, individual movements of digits in exploring, and elevation of one shoulder in evacuating a gorged food pouch. This deficit has been observed to last up to 4 years and thus may be considered permanent. Tower (103) describes such animals as follows.

"The usage which survives, be it posture, progression, fighting, or reaching-grasping, is stripped of all the finer qualities which make for aim, precision and modifiability in the course of execution. These remaining stereotyped performances are useful still, but they are by no means the skilled performances of the intact animal. Inasmuch as the residual performances may require the most intense voluntary attention for their successful employment, as happens after bilateral pyramidal lesion in the adult monkey, the condition cannot be called a complete voluntary paresis. In other words, extrapyramidal action from the cortex may be employed quite as voluntarily as pyramidal action. The selective destruction is of the least stereotyped, most discrete, movements or elements in movement."

Associated with the paresis is a hypotonia, reduced resistance to passive manipulation, which is somewhat more prominent in the monkey than in the chimpanzee. Unilateral lesions affect the abdomen and the extremities most severely. The leg suffers more than the arm, although with bilateral lesions the hypotonia is relatively uniform. At first thought, the relative severity of leg impairment following unilateral lesions is surprising because fiber counts indicate a reduction of 50 per cent after the lateral corticospinal tract has descended below the cervical enlargment (107). Since the contribution to arm segments is

[4] The proximity of the lemniscus makes depth of section critical, and dimpling of tissue under the knife causes uncertainty. By any technique, the lemniscus probably suffers some insult; but the difficulty can be diminished by passing a fine suture under the tract and gently pulling the free ends, passed through a fine glass tube held against the pyramidal surface, until the suture cuts through the tract. Slightly modified, the same technique can be used to transect the bulb for experiments in which it is desired to have only the pyramids in continuity (52).

equal to that supplying the subcervical segments and therefore greater than that exclusively supplying the leg segments, one would expect the arm to be more impaired. The contrary superiority of arm over leg is probably a measure of the effectiveness of the uncrossed paths (39, 60, 89, 93) which supply chiefly the cervical segments.

Superficial reflexes such as the abdominal and cremasteric, and local reactions to pin prick, are severely attentuated or abolished. Deep reflexes are elevated in threshold, slow and full, presumably because they are unchecked by antagonistic reciprocal contraction. Tonic neck reflexes are absent and clonus does not occur. Contact and visual placing reactions and proprioceptive hopping and placing are weak. In both the monkey and the chimpanzee, a forced grasp reflex is prominent, i.e. stretch on the flexor tendons of the digits induces strong digital flexion. This reflex may be so severe that it interferes with climbing, the animal often getting 'hung up' because it is unable to release its grip on the cage bars. Occurrence of forced grasping is surprising since previous cortical extirpation studies suggested that the grasp reflex is released by interruption of 'extrapyramidal' rather than pyramidal fibers (37), and even more so because the other signs of pyramidotomy suggest interruption of an excitatory pathway rather than release of spinal reflex centers from descending inhibitory impulses.

In the monkey the plantar reflex is obtunded, but the pattern is normal (ventroflexion). In the chimpanzee, however, a Babinski sign with dorsiflexion and fanning of the toes is a constant and enduring finding after pyramidal section as it is following lesions of area 4 (38).

In both the monkey and the chimpanzee (but more prominently in the monkey) decreased skin temperatures are consistently found in the paretic extremities, suggesting a tonic inhibitory effect of pyramidal fibers on sympathetic preganglionic neurons (but see 53). Finally, both monkeys and chimpanzees surviving pyramidotomy for 2 months or more show decreased muscle mass in the paretic extremity, and histological examination of the muscle shows atrophy with shrinking of fiber size.

Particular interest attaches to the finding of hypotonia following experimental pyramidotomy in primates because it conflicts with the persistent teaching of clinical neurology that pyramidal tract interruption produces spasticity. This contention has no scientific basis because lesions in man are invariably mixed. There is no known instance of isolated pyramidal tract interruption in man, with the possible exception of the much quoted case described by Hausman (43) in which the resulting paralysis was flaccid or 'flail-like' rather than spastic.

Nevertheless, it may be forcibly argued that bulbar pyramidotomy is not equivalent to total destruction of the cells contributing to the pyramidal system. The proximal portions of the neuron remain intact. The cell bodies show retrograde chromatolysis and reduction in size but do not undergo irreversible degeneration (50); presumably, they remain functional. This type of reaction is characteristic of cells having axons which give off numerous collaterals central to the point of amputation, and there is abundant evidence that pyramidal fibers spawn many collateral branches during their course from the cortex to the decussation. Branches to the striatum, the substantia nigra and the brain-stem reticular formation have been described; but some of these may be 'extrapyramidal' endings rather than pyramidal collaterals. Numerous true collaterals are given off to the pontine nuclei (88, p. 967). In the bulb, particularly at the level of the facial nerve nucleus, many fine collaterals run to the large cells of the medial reticular formation (88, p. 957; Scheibel, A. & M. Scheibel, personal communication).[5] There are, therefore, numerous points at which impulses generated in corticospinal neurons may be fed into descending pathways other than the pyramid, and the distinction between pyramidal and extrapyramidal systems loses functional significance.

All pathways innervated by suprabulbar collateral branches are left intact after pyramidotomy, which amputates only the direct pathway from cortex to spinal cord, and it is quite possible that interruption of the same axons at levels rostral to the collateral branching might yield quite different results. Significantly, Tower (102) found that lesions in the pons (where pyramidal collaterals are profuse), interrupting partially or completely the pontine corticospinal bundle, produced clear-cut spasticity with "exaggerated postural and tendon reflexes, excessive tone of 'clasp-knife' quality, and readily excitable clonus" in monkeys.

It may develop that electrical recording techniques will give further information about the pyramidal collateral pathways which are so difficult to follow with certainty by anatomical techniques. Surface stimulation of the bulbar pyramid should antidromi-

[5] Cryptically in another place (88, p. 890) Ramón y Cajal states that the pyramidal fibers give off no collaterals throughout their bulbar course. Nevertheless, collaterals are shown clearly and labeled as such in several figures (e.g. 88, figs. 409, 431).

cally activate collateral pathways. For example, such stimulation evokes in the bulbar reticular formation and the cervical vagus nerve electrical activity which, on the basis of latency and failure to follow high stimulus repetition rates, traverses at least one synapse (Mahnke, Nelson & Patton, unpublished observations). However, it is difficult to eliminate the possibility of stimulus spread to the adjacent lemniscus and reticular formation and thus clearly to implicate pyramidal collaterals.

STIMULATION OF THE PYRAMIDS

Since the discovery of the motor cortex by Fritsch & Hitzig (35), the movements resulting from stimulation of cortical motor foci have been repeatedly studied and mapped (see the preceding chapter). Valuable as such studies are, they do not give clear information (as is commonly erroneously supposed) on the role of corticospinal function. Cortical stimulation obviously excites 'extrapyramidal' as well as pyramidal pathways (80), and strong participation by the former in initiating movement is indicated by the fact that cortical stimulation provokes movement after chronic pyramidotomy (100). To study the pyramidal contribution to movement requires stimulation at the bulbar level where the tract is uncontaminated. Movement patterns resulting from bulbar pyramidal stimulation were analyzed by Brookhart (18) and by Landau (52), using multiple electromyography in monkeys anesthetized with barbiturates and in decerebrate cats. Such preparations have the advantage that descending pathways activated by antidromic invasion of pyramidal collaterals in the pons are not excluded but present the disadvantage that the hazard of stimulus spread to adjacent structures is uncontrolled. This difficulty can only be circumvented by stimulation rostral to a bulbar transection sparing only the pyramids (72) and sacrificing collateral pathways.

A striking characteristic of pyramid-evoked movement is the need for temporal summation; electromyographic signs of contraction occurred only when the pyramid was repetitively shocked. In the monkey (18), the duration of a train of given frequency and pulse duration required to produce contraction is characteristic for a particular muscle and varies for different muscles; reducing the threshold train by a single pulse prevents onset of contraction. For all muscles, increasing the frequency of stimulation decreases the train duration needed to produce contraction. Increased pulse duration markedly shortens the train-duration threshold for proximal muscles but is much less effective in shortening the train-duration threshold for distal musculature, e.g. hand and finger. Direct recording from the pyramid indicates that the greater effectiveness of long (2.0 msec.) compared to short (0.1 msec.) pulses is largely attributable to recruitment of slowly conducting (hence presumably small-diameter) fibers by the longer pulses. It may thus be argued that the larger fibers are primarily concerned with the control of distal musculature and the more numerous, small fibers with the larger proximal muscles (18).

Landau (52) stresses the variability of movement patterns elicited by pyramidal stimulation in decerebrate cats. In different animals and from time to time in the same preparation, the sequence of muscle activation varied independently of such controllable factors as anesthesia, posture, and locus and parameters of stimulation. Landau ascribes this variability to the spinal internuncial system on which the pyramidal efferents play. Although the internuncials interposed between pyramidal endings and motoneurons undoubtedly modulate the transfer of impulses (72), some of the variability of Landau's experiments is more readily explained by assuming varying spread of stimulus to adjacent structures. For example, the organized movements ('walking, batting, digging, scratching') that occurred resembled more the reflex results of afferent stimulation than the response to stimulation of an efferent pathway. The latter possibility is particularly unlikely because, although there is evidence that individual pyramidal fibers arising from different topographically organized cortical areas do not overlap extensively in their spinal distribution (26), these fibers are thoroughly mixed at the bulbar level (6, 77, 103). Thus, the chance that stimulation at this level would excite fibers selectively and in the proper temporal sequence to produce complex, organized movements appears remote. On the other hand, stimulus spread to the lemniscus, with collateral activation of the reticular formation, might well generate such reflex patterns.

In addition to contraction of skeletal muscle, pyramidal stimulation is reported to cause changes in autonomic effectors (53), including sweating (galvanic skin response), piloerection, pupillary dilation, and alterations in arterial pressure, heart rate, intravesical pressure and gastric rhythms. Although the responses were said to be abolished by pyramidotomy below the point of stimulation, the variability in response raises again the question of stimulus spread.

Although the physiological role of the pyramidal tract remains problematical, the results of pyramidotomy and of pyramidal stimulation permit some general conclusions. First, it appears clear that voluntary movement is less dependent on pyramidal function than is commonly supposed; the special contribution of pyramidal impulses appears to be fine, precise control, particularly of the distal musculature. Secondly, apart from reciprocal effects, the preponderant spinal action of impulses traversing the pyramids appears to be excitatory. There remains the distinct possibility, however, that suprabulbar collaterals of descending excitatory axons may feed into descending systems which have an opposite effect on the excitability of spinal motoneurons.

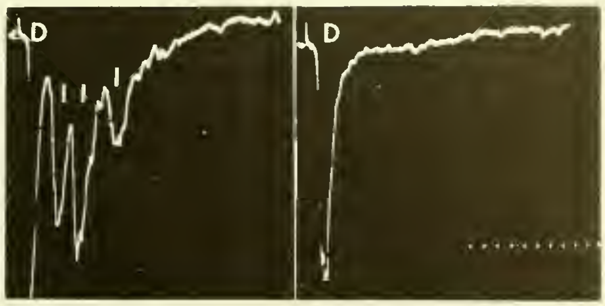

FIG. 2. Pyramidal tract responses to stimulation of the motor cortex and white matter in monkey (Dial anesthesia). Recording electrode in lateral column at C_1. Downward deflection in this and all subsequent figures indicates positivity at the exploring electrode. *Left*, stimulus to the contralateral motor cortex; D and I waves are labelled. *Right*, stimulus to white matter after ablation of motor cortex; only the D wave persists. Time, 1 msec.

CORTICAL EXCITATION OF PYRAMIDAL TRACT

Although direct cortical stimulation has been extensively used to study motor areas since 1870, recording from the pyramidal tract was not attempted until the pioneering studies by Adrian & Moruzzi (1) in 1939. Unfortunately, they chose to record from the region of pyramidal decussation and, consequently, their recordings were contaminated with activity of the bulbar reticular units through which the decussating pyramidal fibers pass (80). Electrodes placed in the bulbar pyramid or the lateral column of the cord[6] record a characteristic configuration when a single shock of short duration (0.1 msec.) is applied to the cortex (80). The initial deflection is a stable positive wave (fig. 2) with a latency of about 0.7 msec. at the bulbar level and about 1 msec. at cord segment C_1; this is followed, some 2.0 to 2.5 msec. later, by a series of variable positive deflections which recur at intervals of about 2.0 to 2.5 msec. The initial deflection occurs after a latency too brief to allow both conduction and synaptic transfer, readily follows stimulus repetition rates up to 400 to 500 per sec., and can be elicited by stimulation of white matter after removal of the cortex (fig. 2). This deflection therefore represents activity directly initiated in Betz cells[7] by the cortical shock and accordingly is called the D wave. The deflections following the D wave vary in amplitude, fail to follow high stimulus repetition rates, and are more susceptible than the D waves to asphyxia, anesthesia and cortical injury. All these properties suggest activity resulting from synaptically relayed excitation of Betz cells, and the late waves are therefore referred to as I (for indirect) waves.

In our original analysis we suggested that the I waves were not significantly contaminated by activity of directly excited, slowly conducting fibers because the pyramidal response to white matter stimulation failed to reveal much late activity (figs. 2, 3). Nevertheless, both anatomical (20, 62) and functional (13) studies indicate the presence of many slowly-conducting fibers in the pyramids. Moreover, Patton & Towe (unpublished observations) have isolated a few cortical units capable of following antidromic pyramidal stimulation rates up to 100 per sec., which have bulb-to-cortex conduction times up to 7 to 8 msec. Directly-evoked activity in such slowly-conducting units may well reach the pyramid simultaneously with I activity of more rapidly-conducting units. However, it is quite clear that directly-excited fibers of slow conduction rates can account for only a small amount of the I activity.

The cellular elements that bombard the Betz cells to produce I discharges are located in the cortex, for there are no I waves in the pyramidal discharge evoked by stimulation of the white matter after the

[6] Cord recording also carries the hazard of contamination of response. All critical observations reported here have been carefully checked by bulbar recording.

[7] It is unfortunate that there is no acceptable term for cortical cells projecting into the pyramid; the term 'Betz cell' presumably applies only to the largest of such cells, although the size limit has never been clearly defined (106). In any case, cells with cross-sectional areas of 900 to 1400 μ^2 account for only a small percentage of the pyramidal axons; hence, many smaller cells must contribute. In this discussion, the term 'Betz cell' has been used to indicate any cortical cell, irrespective of size, with the axon transversing the pyramid.

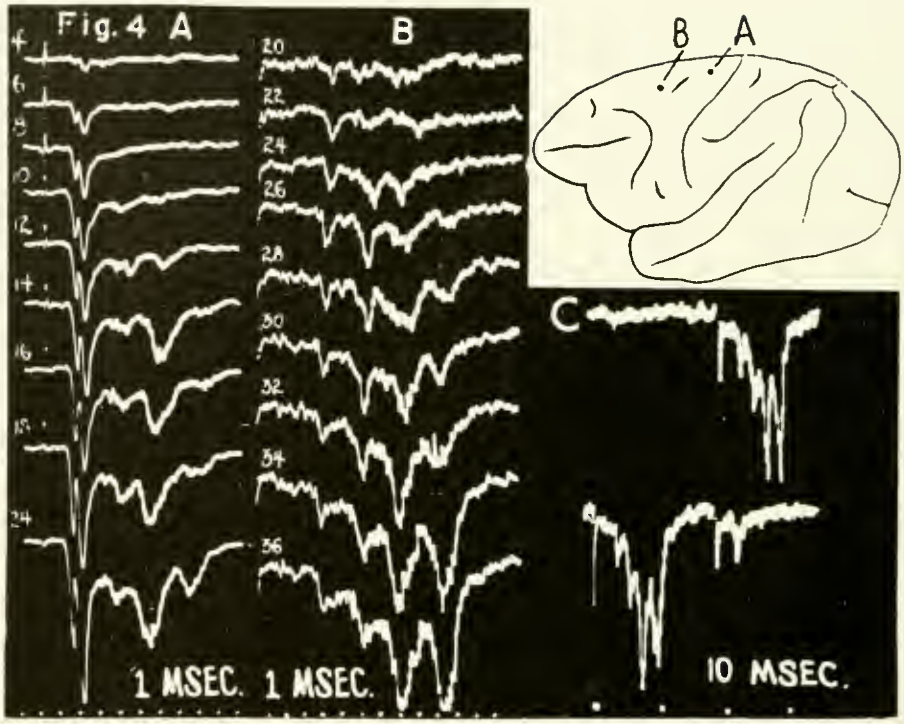

FIG. 3. Pyramidal complexes evoked by stimulation at various levels beneath cortical surface in monkey (Dial anesthesia). Recording electrode in contralateral lateral column between C_1 and C_2. Stimulus through focal monopolar electrode on, within or beneath contralateral motor arm area. *Numbers* under each trace indicate depth of stimulating electrode in millimeters, measured from cortical surface. Cortex was 2.5 mm thick at point of penetration. [From Patton & Amassian (80).]

FIG. 4. Effect of cortical stimulus site and stimulus strength on pyramidal discharge in monkey (Dial anesthesia). Recording electrode below C_1 in the lateral column contralateral to stimulation. *A*. Responses elicited by stimulating point A (*inset*) with relative strengths indicated by numbers under the traces. *B*. Responses evoked from point B; note high threshold compared to *A*. *C*. Responses evoked by stimulating point B; *upper trace*, test response alone; *lower trace*, test shock followed identical conditioning shock by 18 msec. Note in test response there is obliteration of late (I) activity but persistence of the component with latency of 4 msec. (slowly conducted D wave). [From Patton & Amassian (80).]

cortex has been removed (fig. 2). In the experiment shown in figure 3, the cortex was left intact, but the stimulating electrode was thrust for varying distances into or through the cortex, which was 2.5 mm thick. Deep in the white matter (lower trace) only the D wave was evoked; as the stimulating electrode was pulled into and through the gray matter, I waves appeared and were maximum at a depth of 2.0 mm. Incidentally, this experiment eliminates the possibility that I waves recorded under barbiturate anesthesia result from re-excitation via the recurrent collaterals of Betz cells (23, 25, 74). Stimulation in the white matter should invade such collaterals antidromically, producing I activity, but the lower trace shows little or no late activity. More pertinent arguments against the participation of recurrent collaterals in the re-excitation of Betz cells are given below.

Thus, the I waves of a cortically evoked, pyramidal discharge result from relayed excitation of Betz cells via cortical interneurons, and the size of the waves provides a convenient and reliable measure of cortical excitability (12, 21, 80, 105, 114). The question arises whether the units synaptically fired during I activity are those which were directly fired to produce the D wave. Inspection of figure 3 provides a partial answer; the area of the third I wave in the fourth trace from the top is considerably greater than that of the D wave; hence, even assuming some sharing of units in

D and I, the conclusion is inescapable that the units firing during the I wave outnumber those active during the D wave. Therefore, at least some of these indirectly-excited cells must have escaped direct excitation. The same thing is shown even more clearly in figure 4, where the responses to stimulation of a focus in area 4 are compared with those evoked by stimulation of a point rostral to area 4. The latter are characterized by a small, late (4 msec.) D wave, followed by a series of I waves each of which has a far greater amplitude and area than the D wave. It must thus be concluded that the cortical interneuron system diffuses excitation through the cortex and excites some Betz cells situated too far from the stimulating electrodes to be directly excited. The significance of this for cortical mapping is discussed below.

To answer the rest of the question, i.e. do cortical interneurons cause repetitive firing of some cells directly fired, requires single unit recording from pyramidal axons or Betz cells. Occlusive interaction (with 50 per cent reduction) of a test D wave timed to fall during a conditioning I discharge can be demonstrated (80, fig. 7), but this evidence is not conclusive because distinction between occlusion and inhibition is uncertain. Figure 5*A* shows the response of a single pyramidal axon to a weak cortical shock; two spikes occurred, the first having a latency of about 3 msec. The lower trace (*B*) shows that at a stimulus repetition rate of 430 per sec. the unit failed to fire, suggesting that it was indirectly excited. In *C*, the stimulus strength was increased (thus enlarging the effective area of the stimulus). The unit then fired four spikes, the first with a latency of about 1.2 msec. Trace *D* shows that this early spike followed a stimulus of 430 per sec., and hence the unit must have been directly excited. Brookhart (19) found that pyramidal axons stimulated in the cord, even with strong shocks of 2 msec. duration, do not fire repetitively, a fact suggesting that the last three spikes of trace *C* reflect synaptic excitation of a cell previously fired directly by the stimulus. Recording with intracellular electrodes, Phillips (86) also noted direct and relayed firing of the same Betz cell to long (10 msec.) cortical shocks. Thus, cortical interneurons cause repetitive firing of Betz cells near the stimulating electrodes and initiate delayed firing of cells outside the directly effective orb of the electrodes.

The interval between the D wave and the first I wave should provide an estimate of synaptic delay in the cortex. Indeed, the experimental arrangement is comparable to that employed by Lorente de Nó (73) to determine synaptic delay in the oculomotor nucleus.

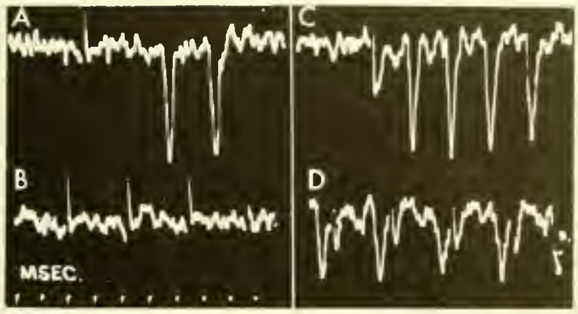

FIG. 5. Pyramidal axon spikes in a cat anesthetized with chloralose and given tubocurarine. Recording electrode in lateral column between C_1 and C_2. *A*. Response to weak contralateral precruciate stimulus. *B*. Sweep taken during stimulus train at 430 per sec. and same strength as in *A*. *C*. Response to stronger stimulus than in *A*; note addition of early (2 msec.) spike. *D*. Sweep during stimulus train at 430 per sec.; strength as in *C*; short-latency spike follows stimulus rate. [From Patton & Amassian (80).]

In preparations in which D and I waves are recognizably distinct (figs. 3, 4), the time interval is usually of the order of 2.0 to 2.5 msec. As an estimate of synaptic delay, this interval is about double that given by other sources. One possible interpretation of I wave periodicity is based upon two assumptions. First, that Golgi type II cells are responsible for synaptic excitation of Betz cells. Second, that longitudinally orientated neurons are more easily excited by an electric stimulus applied to the cortical surface than are the compact field Golgi type II cells. An electrical stimulus to the cortex would then excite Betz cells and other longitudinally oriented cells directly. The latter would subsequently excite Betz cells through the intermediary Golgi type II cells. The over-all delay for the indirect excitation of Betz cells following electrical stimulation would thus be two synaptic delays or a multiple thereof. In the monkey, the rather regular recurrence of I waves, again at intervals of 2.0 to 2.5 msec., suggests periodic bombardment of the Betz cells through chains of neurons with fixed temporal characteristics. Often, the I waves increase progressively in amplitude (figs. 3, 4*B*) perhaps reflecting avalanche conduction in the longer chains. In the cat anesthetized with chloralose, however, the I activity often begins on the tail of the D wave and persists for as long as 15 to 20 msec. as a slowly waning discharge without clear maxima, a configuration suggesting an asynchronous discharge through chains with varying temporal characteristics (80).

ORIGIN OF PYRAMIDAL TRACT

That the pyramidal tract arises entirely from cortical neurons is now established in man (61) and monkey (76), in which hemispherectomy causes complete degeneration of longitudinally descending axons in the pyramid. Delineation of specific cortical areas contributing axons to the pyramid has been the goal of many anatomical investigators using retrograde and secondary degeneration techniques. These studies have been summarized by Tower (103) and Lassek (59, 60). The giant pyramid-shaped cells of Betz, particularly prominent in the fifth layer of the precentral gyrus, undergo unmistakable chromatolytic changes and atrophy following interruption of the pyramid (47, 63, 64, 91, 111). Contrary to oft-repeated statements in unsophisticated textbooks, however, it is perfectly clear that the large, pyramid-shaped cells account for only about 2 to 3 per cent of the axons in the bulbar pyramids. In man, Lassek (56) counted only 34,000 giant pyramid-shaped cells with cross-section areas ranging from 900 to 4100 μ^2; whereas the bulbar pyramid contains about 1 million axons (62). In the monkey, a similar ratio obtains, 18,845 cells (600 to 3000 μ^2) to 500,000 fibers (57). If the reasonable assumption that large cell bodies give rise to large axons is accepted, it may be supposed that the large Betz cells are the parents of the 30,000 myelinated pyramidal axons, which range in diameter from 9 to 22 μ (62). The much more numerous small myelinated pyramidal axons (almost 90 per cent are less than 4 μ in diameter) and the unmyelinated axons (which comprise roughly 40 per cent of the total) must arise from smaller, less distinctive cortical elements. The density of giant Betz cells varies in the different topographical subdivisions of area 4, 75 per cent being found in that for the leg, 17.9 per cent in that for the arm and 6.6 per cent in that for the face (56).

Pyramidal axons arise largely from cells in the internal lamina (74). In single-unit recording of cortical cells of cats, Patton & Towe (unpublished observations) found corticopyramidal units (identified by their ability to follow high-frequency antidromic pyramidal stimulation) in all layers except I and II, but the greatest density was in layers V and VI. Seventy-one such cells were distributed as follows: layer III (depth, 500 to 870 μ), 6; layer IV (870 to 1070 μ), 6; layer V (1070 to 1370 μ), 24; and layer VI (1370 to 1900 μ), 35.[5] There was no significant correlation between the relative size of a unit (as estimated from the bulb-to-cortex conduction time) and its apparent depth location. Depth location in cortical unit analysis is, of course, subject to some inaccuracies, which are discussed at length below.

The contributions of different cytoarchitectural areas to the pyramid have been investigated intensively. Lassek (58) found that ablation of area 4 caused degeneration of 27 to 40 per cent of the pyramidal axons in monkeys. Virtually all of the largest myelinated pyramidal axons degenerated. Häggqvist (42) found only a 20 per cent loss after such lesions. It is not clear that the cortical lesions in these studies included the entire supplementary motor area on the mesial surface (113). Fiber counts have not been made following combined lesions of areas 4 and 6, but Welch & Kennard (108) noted that pyramidal degeneration was incomplete. About half the pyramidal fibers degenerate after combined pre- and postcentral ablation (58), and Peele (83) noticed pyramidal degeneration (Marchi and Weigert stains) following lesions of areas 1, 2, 3, 5 and 7. In cats, degeneration studies with Glees' silver method suggests pyramidal contributions from the temporal and occipital cortex (104), a finding so surprising that it should be further investigated. In summary, it may be said that degeneration studies of different sorts and by different investigators give a confused picture with contradictory elements, but all agree that the classical motor cortex of area 4 is not the sole source of pyramidal fibers.

Studies in which electrical recording is used to localize pyramidal origins generally reveal a somewhat more restricted cortical pattern. Since the presence of a D wave in cortically evoked pyramidal discharges indicates that corticospinal neurons lie within the effective radius of the stimulating electrodes, mapping the cortical regions from which D waves can be evoked might be expected to yield a picture of the areal origin of corticospinal projections. Because effective stimulus radius depends on stimulus strength, such maps err, if at all, in the direction of overextensiveness. In cats, Patton & Roscoe (unpublished observations), using this method, found two distinct projection zones. The first includes the anterior sigmoid gyrus and that part of the posterior sigmoid gyrus corresponding to the leg and arm subdivisions of somatosensory area I. The second is in the anterior ectosylvian gyrus and is roughly coextensive with the arm and leg subdivisions of somatosensory area II. An isthmus of cortex, either silent or yielding only I activity, extends over part of the coronal gyrus between the two projection areas and corresponds to the

[5] Depth ranges for individual layers are mean values taken from frozen sections of arm somatosensory area I; paraffin sections shrink too much for accurate measurement (67).

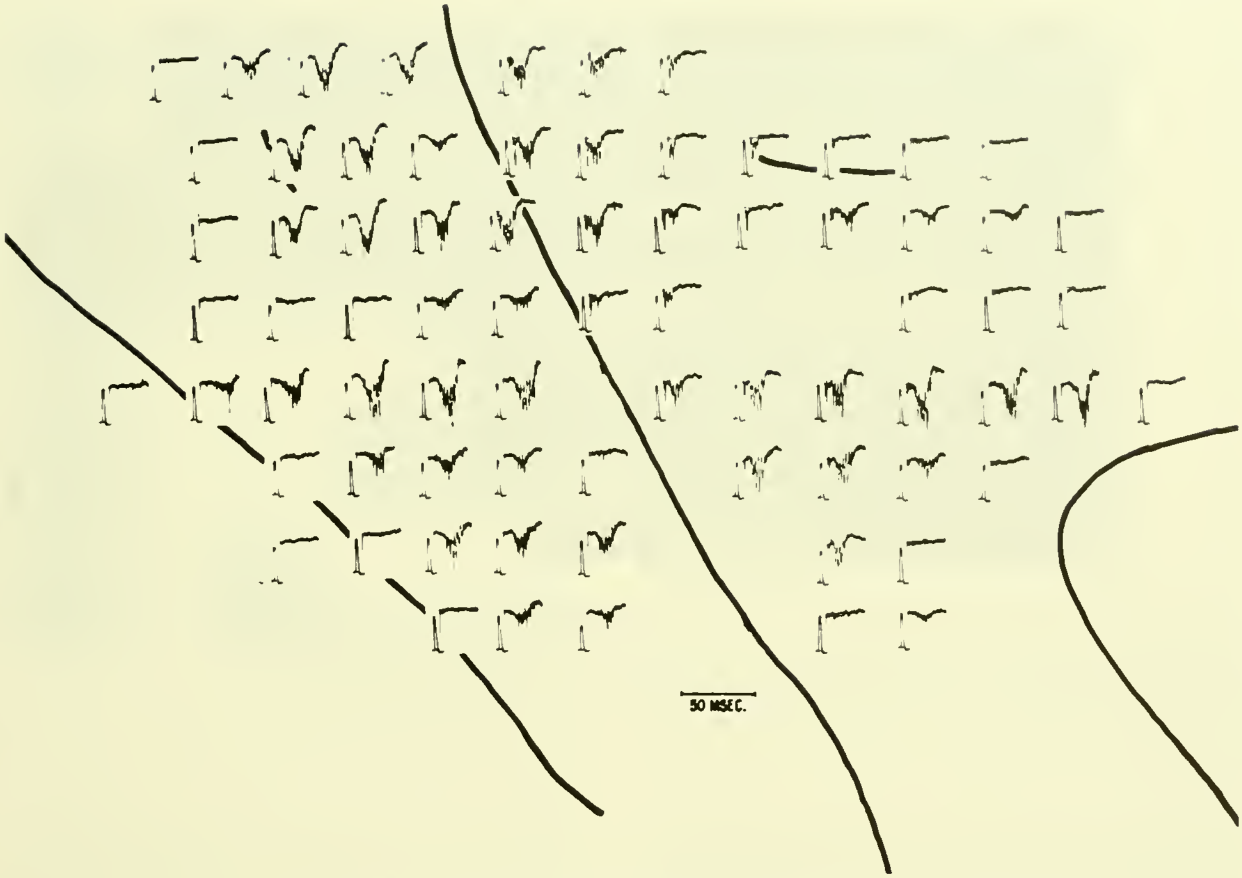

FIG. 6. Map of pyramidal responses evoked by stimulating different cortical foci in Dial-anesthetized monkey. Responses recorded from contralateral spinal cord (C_2) are superimposed on stimulus foci. Pulse below each trace is stimulus current, which was kept constant (except in one of the lower traces) at 6 ma (duration, 0.1 msec.). Major cortical markings from *left* to *right*: intraparietal sulcus, central sulcus, arcuate sulcus.

face receiving zone. Direct pyramidal responses from the face cortex are presumably excluded by bulbar recording. The data agree approximately with those of Lance & Manning (51).

Surrounding the regions from which D activity can be elicited is a fringe, variable in extent, from which only I activity may be evoked. Presumably these regions have few or no pyramidal projections but are connected with projection areas through cortical interneurons. The size of the 'I fringe' is variable but is most extensive under light anesthesia.

In the monkey (81), the major projection zone is precentral (fig. 6); stimulation on the postcentral gyrus and the parietal cortex elicits a pyramidal response which is dominated by I activity, and which is largely abolished by removal of the precentral gyrus (fig. 7). This is surprising in view of the anatomical claim that the postcentral and parietal cortex contribute axons to the pyramid; it is possible that such contributions are derived from small cells not easily excited by the rather weak stimuli employed in the mapping experiments.

A feature of interest is the very extensive I fringe in the lightly anesthetized monkey (figs. 6, 7, 9). Even with weak stimulation (far below the threshold for movement), pyramidal projection cells are excited by shocks applied to cortical areas remote from the main projection areas. Such connections between remote zones and motor projection areas, although not surprising, raise problems in the interpretation of mapping experiments in which muscle contraction is used as an end point. Firstly, the strength of stimulus required to produce movement incurs extensive physical spread of stimulating current; indeed, Phillips (86) found that single shocks in the motor cortex of the cat sufficient to produce movement (10 msec. pulse, 740 amp.) caused direct firing of Betz cells virtually throughout the motor cortex. Quite apart from

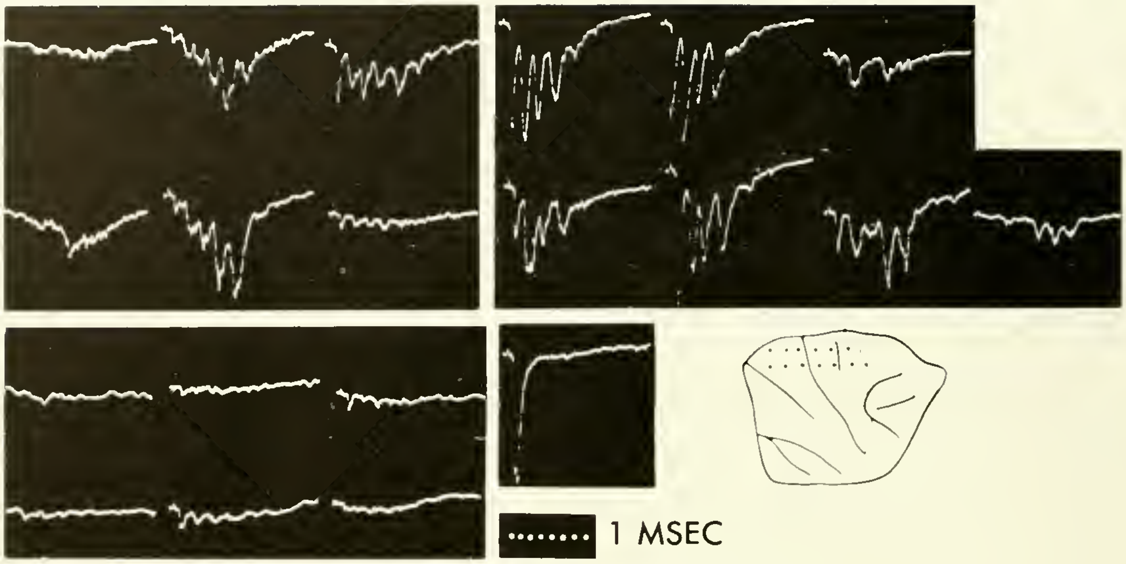

FIG. 7. Effect of precentral ablation on cortically evoked pyramidal discharges in monkey (Dial anesthesia). Recordings from contralateral spinal cord (C_1). *Upper set of traces* shows responses to stimulating six postcentral and seven precentral foci shown in *inset* at *right*. *Lower set of traces* shows responses from stimulating same postcentral foci after ablation of cortex enclosed by *dotted line* in *inset*. *Right lower trace* is recording following stimulus to precentral white matter exposed by ablation.

physical spread, neural spread, as indicated in figures 6 and 7, is extensive. Figures 8 and 9 show that even under barbiturate anesthesia such neuronal spread may cross functional as well as anatomical boundaries; in this experiment, the leg area was mapped while the recording electrode was installed in the lumbar lateral column. Lumbar D waves were recorded only following stimulation of the medially situated leg subdivision, but shocks in the arm subdivision caused appreciable indirect firing of Betz cells having impulses which were destined for lumbar segments.

It seems likely that such interareal spread accounts for some of the confusion concerning the topographical organization of the motor cortex (69, 70). Strong stimulation and light anesthesia mask discrete cortical representation by favoring interareal spread. In unanesthetized monkeys (an ideal preparation for interareal spread), Lilly (71) evoked movements by stimulating virtually any part of the cortex, including visual and auditory receiving areas. While some of the explored regions may provide sufficient 'extrapyramidal' projections to account for the observed movement, it is also likely that interareal connections with pyramidal projection zones participate. If this be true, the wisdom of designating such areas 'motor' may be questioned, for they are really afferent to the projection areas.

Another method of delineating the pyramidal projection areas of the cortex consists of mapping the cortical responses to antidromic stimulation of the bulbar pyramid (fig. 10). This method was first used by Woolsey & Chang (112) and has been used repeatedly by others (24, 51, 55). In the cat, the maps agree fairly well with those obtained by orthodromic stimulation. Landau (55) questions the extent of the projection zone into the postcruciate cortex, ascribing the potentials recorded in somatosensory area I to a combination of volume pickup from precruciate projections (this is diminished by differential recording between the cortical surface and white matter) and stimulus spread to the medial lemniscus. While both of these factors are undoubtedly likely to complicate antidromic potential configurations, there is no doubt that somatosensory area I contributes a significant number of axons to the pyramid in the cat. Using microelectrode unitary recording techniques, Patton & Towe (unpublished observations) found that of 310 cortical units isolated within the arm subdivision of area I, 79 could be fired antidromically by pyramidal stimulation.

In the monkey, maps of pyramidal projections (fig. 10) derived from antidromic stimulation reveal a more extensive pattern than that indicated by mapping D wave sources (figs. 6, 7). The largest potentials

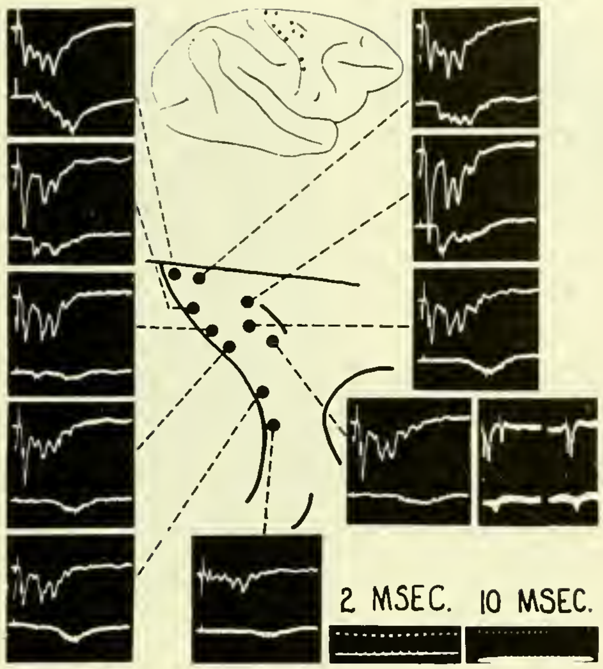

FIG. 8. Simultaneously recorded pyramidal responses from the lateral column between C_1 and C_2 (*upper traces*) and the lateral column between L_2 and L_3 (*lower traces*) in the monkey (Dial anesthesia). Stimulus foci in precentral gyrus shown in *drawing* above and enlarged *sketch* below. Note that stimulation of foci below the superior precentral dimple yields only I waves in lumbar lead. Picture above 10 msec. time scale shows responses to single shock *on right*; to two shocks *on left*. Lumbar test response is obliterated; cervical test response reduced to D component.

were found in the precentral gyrus and the rostral part of the postcentral gyrus, but small deflections were recorded from the entire parietal lobe and from the cortex rostral to area 4. The reasons for the discrepancy between the results obtained by the two methods is not clear, but the complexity of the antidromic potential wave and the possible errors described by Landau (55) indicate the need for further work.

ACTIVATION OF PYRAMIDAL TRACT BY CORTICOPETAL AFFERENT SYSTEMS

Direct cortical stimulation is an unnatural means of exciting the pyramidal tract. A more nearly natural approach is to excite Betz cells via corticopetal (thalamocortical, callosal, etc.) pathways. As first shown by Adrian & Moruzzi (1), in cats anesthetized with chloralose, a volley fired into the ascending systems, evoked by a shock to a peripheral nerve or to skin, generates a corticofugal discharge which can be recorded from the bulbar pyramid. The input to the cortex may be monitored by lemniscal, thalamocortical or surface cortical recordings; the cortex may thus be analyzed as a reflex center. Figure 11*A* shows the responses to superficial radial nerve stimulation recorded by an electrode inserted to the positions shown in figure 11*B* and *C*. When the electrode is in the pyramid, the response usually consists of a simple positive or positive-negative wave of smooth contours suggesting asynchronous firing of pyramidal axons over a period of 15 msec. or more. Each pyramid discharges to a stimulus delivered to either side of the body, but the ipsilateral response is usually more labile and of longer latency (15 to 20 msec. for forelimb) than the contralateral response (10 to 12 msec.). Both ipsilateral and contralateral responses are readily abolished by asphyxia, barbiturate injection or an undercutting of the sensorimotor cortex ipsilateral to the recording site (fig. 12). Volleys originating in the hind limb, the forelimb, or in cutaneous or muscle branches of nerve trunks are equally effective in provoking the discharge.

When the electrode is inserted dorsal to the pyramid, the corticofugal discharge is smaller, but an early deflection appears about 5 msec. earlier (figs. 11, 19). Sometimes this early deflection is recorded when the electrode tip is in the pyramid (particularly if a deep puncture has previously been made), but it is always of maximal amplitude when the electrode is about 1.5 to 2.0 mm dorsal to the pyramidal surface. Since this is the location of the medial lemniscus, the early deflection is reasonably ascribed to ascending lemniscal impulses rather than to a 'pyramidal afferent system,' as described by Brodal & Kaada (16). In barbiturate-anesthetized or decorticated preparations in which the corticofugal discharge is lacking, the lemniscal discharge may be recorded in isolation (fig. 12).

The pathways for the ipsilateral corticofugal discharge are of interest because the afferent pathways to the sensory cortex are thought to be crossed for the most part. Chronic ablation of somatosensory area II, which receives an uncrossed input, does not abolish the pyramidal discharge to ipsilateral sensory stimulation. Although a callosal volley is capable of initiating a pyramidal discharge, the ipsilateral response to forelimb afferent stimulation is independent of the contralateral hemisphere because ipsilateral responses persist in chronically hemidecorticate cats. The ipsilateral response must therefore depend on an uncrossed afferent pathway to the cortex. That the uncrossed pathway is capable of exciting cells in soma-

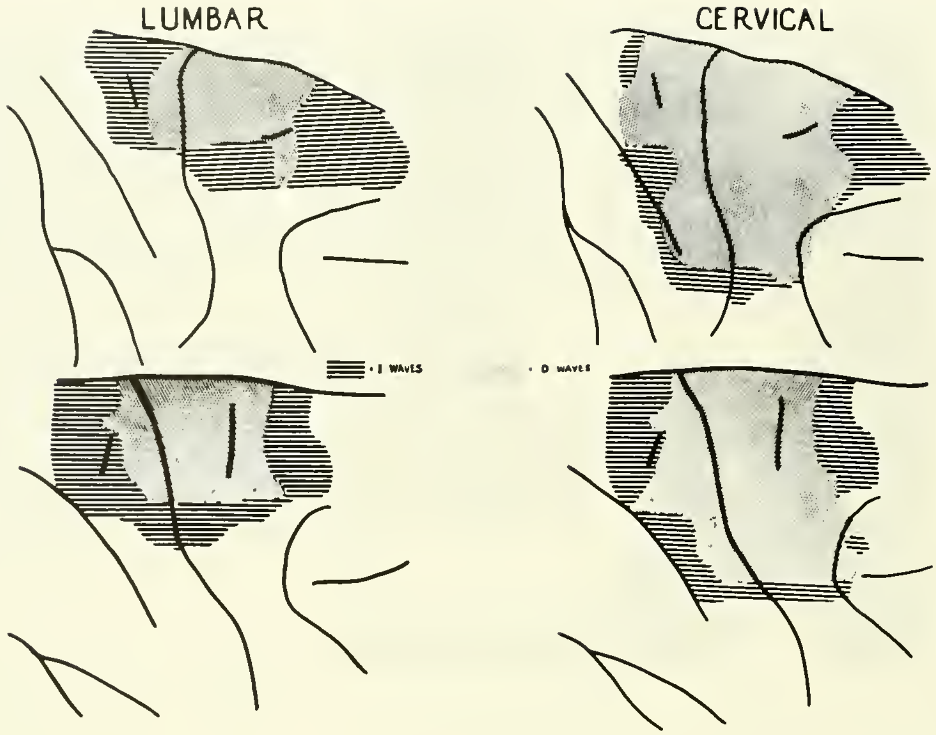

FIG. 9. Maps from two monkeys (Dial anesthesia) showing cortical regions from which pyramidal responses were evoked in the lateral column at L_1 (*left*) and the lateral column at C_1 (*right*) obtained with different stimulus intensities. Responses from stimulating *stippled regions* showed both D and I waves, those from areas with *horizontal bars* only I waves. Stimulus (0.1 msec.) monitored and kept constant throughout; *upper map*, 41.5 ma; *lower map*, 59 ma. D waves from the postcentral gyrus probably resulted from current spread.

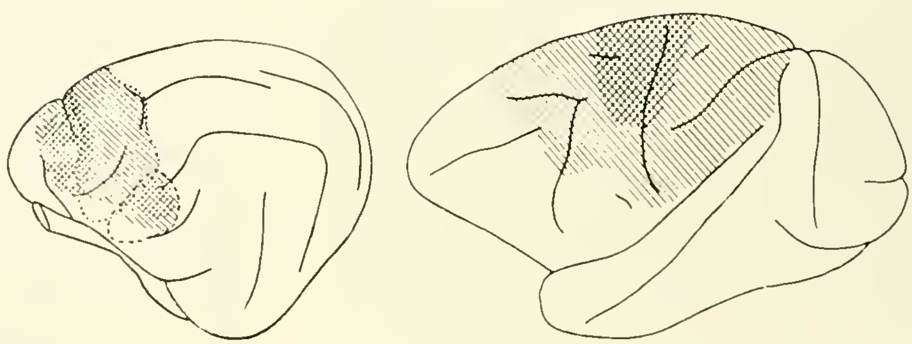

FIG. 10. Cortical regions from which antidromic potentials are recorded following stimulation of bulbar pyramid in cat (*left*) and monkey (*right*). *Heavily hatched areas*, large responses; *lightly hatched areas*, small responses. [From Woolsey & Chang (112).]

tosensory area I is shown in figure 13 in which a Betz cell was fired by either contralateral or ipsilateral forepaw stimulation. Whether recorded as unitary responses (fig. 13) or as multiunit pyramidal discharges (figs. 11, 19), the ipsilateral response is characteristically more fragile and variable and has a longer latency than the contralaterally evoked discharge. In single-unit recording, lower firing probability and greater variation in the number of spikes in the train and in the latency of the first spike distin-

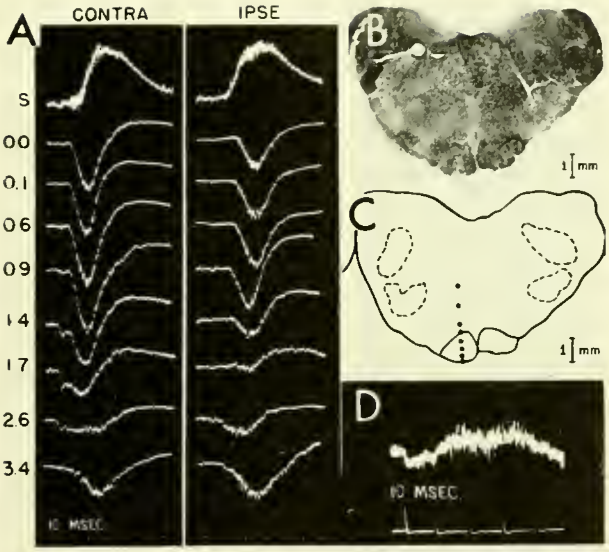

FIG. 11. Bulbar responses to stimulating the contralateral and ipsilateral radial nerve in cat (chloralose-decamethonium anesthesia). *A. Upper traces* (*S*) recorded from the surface of the bulbar pyramid at level shown in *B. Subsequent traces* show responses recorded at depths (millimeters) from surface indicated by *numbers at left*. Recording sites are reproduced in *C. D.* Surface response to ipsilateral forefoot stimulation in another preparation showing notching of negative wave.

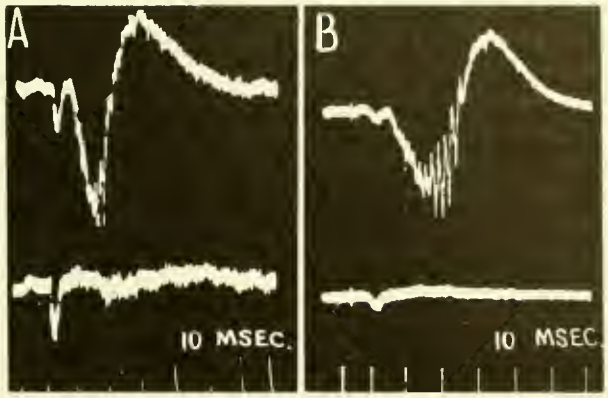

FIG. 12. Effect of cortical injury and anesthesia on pyramidal responses to afferent stimulation in chloralose-anesthetized cats. *A. Upper trace*, response recorded by electrode 0.5 mm beneath surface of bulbar pyramid following stimulus to contralateral ulnar nerve. *Lower trace*, response after undercutting of somatosensory areas I and II. *B. Upper trace*, responses recorded by electrode 0.5 mm beneath surface of bulbar pyramid after stimulus to contralateral forepaw. *Lower trace*, response after intravenous injection of sodium pentobarbital (9.6 mg per kg).

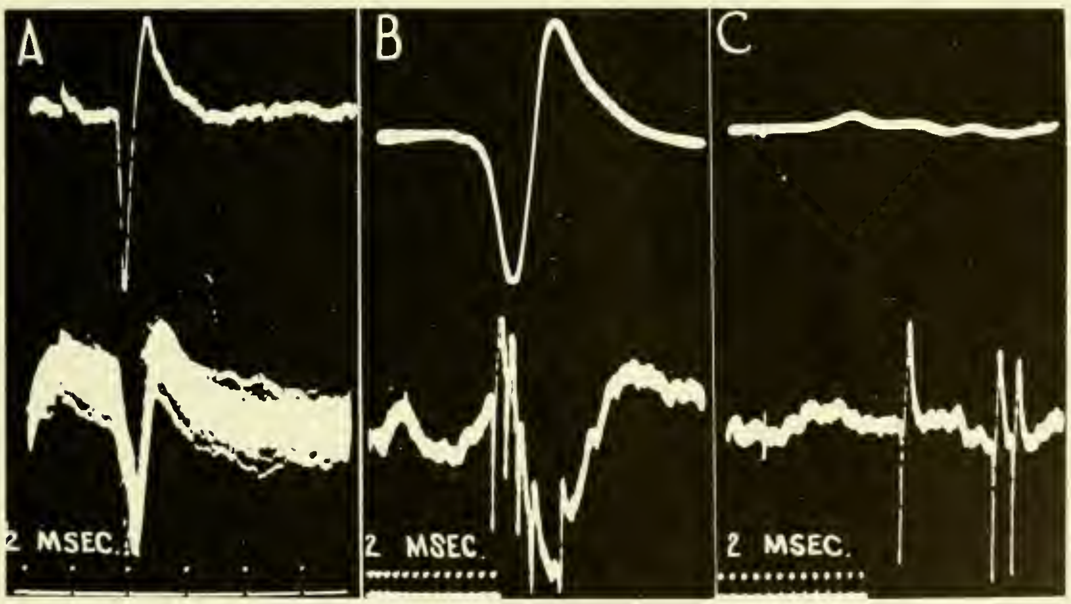

FIG. 13. Spike responses of a Betz cell in arm somatosensory area I to antidromic and orthodromic stimulation in a cat under chloralose-decamethonium anesthesia. *A. Upper trace*, response to antidromic shock (0.01 msec.) to ipsilateral bulbar pyramid. *Lower trace*, superimposed responses to a train of antidromic pyramidal shocks recurring at 100 per sec. *B. Upper trace*, surface cortical response to shock to contralateral forepaw. *Lower trace*, simultaneously recorded spike discharge. *C. Upper trace*, surface cortical response to shock to ipsilateral forepaw. *Lower trace*, simultaneously recorded spike discharge. (From Patton & Towe, unpublished observations.)

guish ipsilateral from contralateral responses. All of these properties suggest that the uncrossed afferent pathway to the Betz cells is less direct (i.e. entails a greater number of synapses) than the crossed pathway.

Conditioning-testing procedures suggest overlap between callosal and thalamocortical pathways to the Betz cells. The pyramidal response to contralateral forepaw stimulation is depressed for 400 to 500 msec. following a discharge elicited by a callosal volley evoked by a single shock to the opposite hemisphere, and a similar interaction occurs when the forepaw shock is used to condition a discharge evoked by callosal stimulation. Similarly, corticofugal discharges elicited by ipsilateral and contralateral forepaw stimulation show depressive interaction (sometimes followed by supernormality) with conditioning-testing shock intervals up to 200 msec. Forepaw-hindpaw (contralateral) tests reveal less interactive depression. Whether the interaction is occlusive or inhibitory has not been determined (2).

In addition to the primary afferent and callosal pathways, the thalamocortical pathway responsible for the augmenting response (31) can elicit a pyramidal discharge which begins during the positive phase of the augmenting wave seen with bulbar recording (21, 79). Stimulation of the pontine reticular formation blocks both the positive component of the augmenting response and the pyramidal discharge (79). Pyramidal discharge is also associated with the cortical spontaneous spindle bursts (14) of barbiturate-anesthetized or sleeping animals (1, 21, 109). In contrast, Brookhart & Zanchetti (21) did not find any pyramidal discharge or change in pyramidal excitability during elicitation of the recruiting response (30) by low-frequency repetitive stimulation of diffusely projecting thalamic nuclei. These authors ascribe Arduini & Whitlock's contrary findings (5) to contamination of the recruiting response with an augmenting response. On the basis of other evidence, Towe (98) has suggested that Betz cells discharge during cortical primary, repetitive and augmenting responses, but not in secondary or recruiting responses.

FIG. 14. Cortical delay of pyramidal discharge in a cat (chloralose-tubocurarine anesthesia). Above are shown responses recorded in the bulbar pyramid (*upper*) and on the surface of somatosensory area I (*lower*) following shock to contralateral ulnar nerve. *Middle* and *lower traces* show D-I complexes recorded in the pyramid following a single shock to area I. *Middle trace*, 10 msec. time scale; *lower trace*, 1 msec. time scale.

TIMING OF BETZ CELL DISCHARGE

Simultaneously recording the pyramidal discharge and the surface cortical response following a shock to a peripheral nerve provides data for estimating the cortical delay in Betz cell excitation. Such an experiment in a cat under chloralose-decamethonium anesthesia yielded the records in figure 14. The upper trace shows the pyramidal response (at the level of the trapezoid body) to stimulation of the contralateral ulnar nerve; the lower trace shows the cortical response simultaneously recorded in somatosensory area I. The pyramidal discharge began 4.6 msec. after the beginning of the cortical response and during its positive phase (4). The middle and bottom records are slow and fast sweeps of the pyramidal response to cortical stimulation, made to determine cortex-to-bulb conduction time, which proved to be 0.52 msec. The cortical delay in Betz cell excitation was thus about 4.1 msec. In other experiments, values ranging from 4.0 to 7.5 msec. were found. Such calculations are obviously only approximate and err in the direction of overestimation of the delay because a minimal conduction time (D wave latency) from cortex to bulb is subtracted. Errors due to conduction time can be eliminated by simultaneously recording the spike activity of individual cortical cells and the surface response. Betz cells can be identified by their ability to follow antidromic pyramidal stimulation at repetition rates of 100 per sec. or greater. (Spikes orthodromically excited by current spread to medial lemniscus do not follow repetitive stimulation at rates exceeding 10 to 20 per sec.)

The Betz cell in somatosensory area I characteristically responds to a single orthodromic volley from the contralateral forepaw with a repetitive burst con-

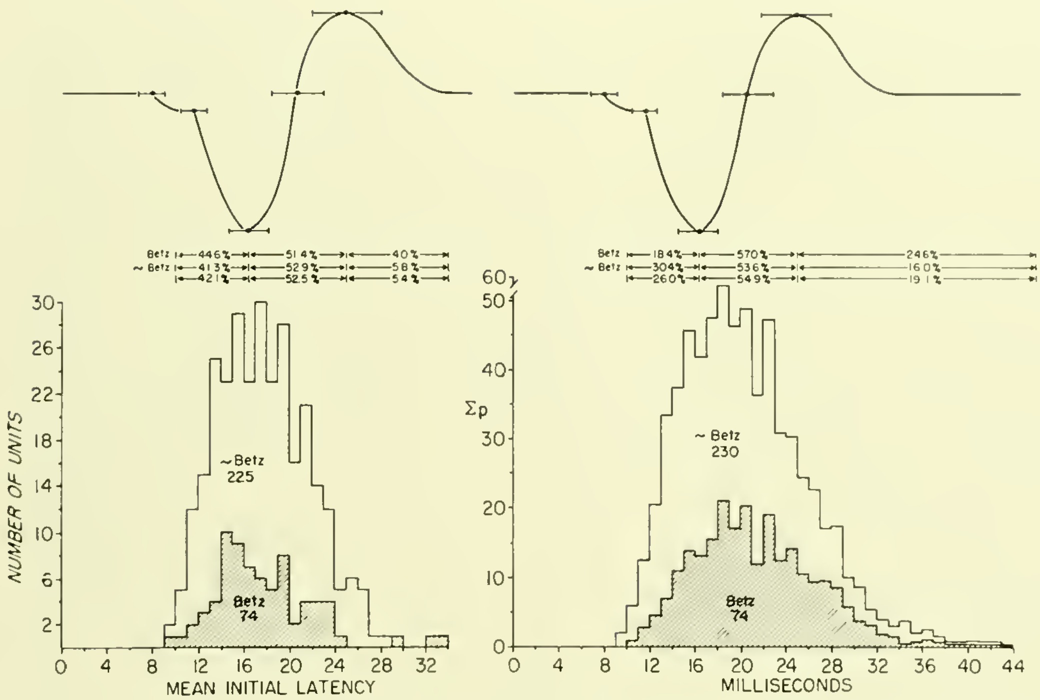

FIG. 15. Firing times of orthodromically excited cortical cells of chloralose-anesthetized cats, related to surface cortical potential. *Left. Upper trace*, reconstructed average surface cortical response (somatosensory area I) to stimulating contralateral footpad; *horizontal brackets* are standard deviations of measured points in time. *Below*, distribution of initial latencies of 132 cortical cells responding to forepaw stimulation; *numbers* bracketed by arrows indicate proportions of Betz, non-Betz and total populations firing first spike within the indicated time periods. *Right. Upper trace*, surface potential as in the left part. *Below*, summation of firing probabilities at indicated times (*abscissa*) for 140 cortical cells. See text. (From Patton & Towe, unpublished observations.)

sisting of 1 to 11 spikes at frequencies up to 500 to 700 per sec. Although other cortical cells often fire repetitively, the mean number of spikes per discharge was significantly greater for 72 Betz cells (3.6) than for 231 cortical cells (1.8) which did not respond to antidromic pyramidal stimulation. For different Betz cells, the latency to the first spike varied from 10.8 to 38.2 msec., and cortical delays (estimated by subtracting latency of surface response from latency of first spike) varied from 2.5 to 30.2 msec. Figure 15 shows the frequency distribution of initial spike latencies for 74 Betz cells and 225 other cortical cells; plotted on the same time base is an average surface reading reconstructed by measuring the points in time in 470 samples from 14 cats. (Amplitude is arbitrary but proportions are approximately correct.)

The surface primary response in cats anesthetized with chloralose consists of an initial positive wave (T), with a mean latency of 7.99 ± 1.11 msec., followed by a larger positive-negative deflection (C), with a latency of 11.61 ± 1.09 msec. Asphyxia or barbiturate anesthesia selectively attenuates or abolishes C but leaves T virtually unaltered. It is suspected (but not proved) that T reflects activity in thalamocortical afferent systems and is thus comparable to the S wave of Perl & Whitlock (84), and that C is associated with postsynaptic cortical firing. Only seven of 310 cortical units discharged during the inscription of T, and the initial discharge of these units was during the latter part of T near the beginning of the C wave. In any case, the beginning of T appears to be the best available measure of arrival of impulses at the cortex.

The numbers between the arrows represent the percentage of the total cellular population which has begun discharging in the time interval bracketed by the arrows. For the Betz cells, considered alone, the following data obtain: before mean peak positivity of C, 44.6 per cent; between mean peak positivity and peak negativity, 51.4 per cent; and later than mean peak negativity, 4.0 per cent. It thus appears that, although a considerable number of Betz cells are

among the cortical cells firing earliest, discharge of a far greater number is delayed until the rising limb of the C wave. This pattern is consistent with the suggestion of Lorente de Nó (75) that corticofugal cells are mainly excited through cortical interneurons interposed between them and the primary afferent plexus in layers III and IV.

The data presented in the left part of figure 15 give only a partial picture of the contributions of cortical cellular spikes to the total cortical activity resulting from an incoming afferent volley because only initiation of firing is represented. Many cortical units (especially Betz cells) fire repetitively in response to a single shock to the foot pad or a peripheral nerve. The discharge train of a Betz cell may occupy 10 to 15 msec. To estimate total contributions for each of 140 recorded units, probabilities of spike discharge (irrespective of the spike position in the train) were computed for each millisecond interval up to 44 msec. after a shock to the contralateral forepaw. Five discharges were measured to compute the probabilities.[9] Summation of the probabilities of individual units gives a measure of the probable number of spikes during each interval. Data from 74 Betz cells and 230 other cortical elements are illustrated in the right part of figure 15, along with the reconstructed surface recording. The greatest spike activity occurred during the intermediate time range between peak positivity and peak negativity of C, but compared to that in figure 15 (*left*), the distribution is skewed to the right, with 19.1 per cent of the total spike activity coinciding in time with the descending limb of the negative portion of C. The firing pattern of the Betz cells considered alone was similar to that of the whole population: 18.4 per cent during the descent of C, 57.0 per cent from peak positivity to peak negativity of C and 24.6 per cent later than mean peak negativity of C.

A more instructive analysis of the spread of cortical excitation involves comparing the activity of units isolated at different depths in the cortex. Unfortunately, with present methods, estimating the depth of units recorded with microelectrodes is subject to several errors which may be serious since the cat somatosensory cortex is only 1800 to 2000 μ thick. For example, dimpling of tissue by the advancing electrode probably makes apparent depth greater than actual depth. This error can presumably be minimized by using fine electrodes or by opening the pia, although the latter procedure certainly entails injury at least to the superficial cortical layers. Also, there is no certainty that recording depth is a valid measure of depth of cell body because volume pickup from distant cells and recording from parts of cells (dendrites) remote from the perikaryon are possible. (Despite vigorous and often apparently judicious argument to the contrary, it must be admitted that the suggested contributions of individual cell parts—dendrites, axons, perikarya—to unitary recordings, whether they be intra- or extracellular, are no better than educated guesses.) In the present account, micromanipulator readings of depth have been assumed to approximate the depth of the cell body.

Figure 16 (*left*) shows the initial latency of units orthodromically fired by shocks to the contralateral forepaw, plotted as a function of depth. Units not satisfying the criteria for Betz cells are shown as dots; Betz units as crosses. The ordinate also shows the average limits of the cytoarchitectural layers as determined from measurements on frozen sections (cf. 67). Within each layer there was considerable spread in latency values as might be expected from horizontal synaptic spread within layers. However, close inspection reveals that latencies tended to be longer in the superficial layers and to decrease progressively to minimum values in layers III and IV (the locus of the thalamocortical specific afferent plexus). This tendency is shown more clearly in the right half of figure 16, where the mean initial latency for each layer is plotted. The progressively increasing firing latency toward the surface from layers III and IV accords with the temporal and spatial pattern of the spread of electronegativity measured with gross penetrating electrodes (4; Towe, unpublished observations).

It has been argued (4) that the rate of progression of maximal negativity is too slow to be accounted for by conduction through apical dendrites at reported characteristic conduction rates (22–24). That the spread to the surface is synaptic is further suggested by the fact that there is an inverse relation between initial latency and maximal repetitive rates which cortical units will follow faithfully, failure to follow high rates of stimulation being characteristic of cells activated via multisynaptic pathways.

Activation of the internal lamina is more complex; units in layer V are activated later than those in layers III and IV, suggesting synaptic spread of activity downward; but layer VI contains a population of units (some Betz cells, some not) which fire with brief delays. The differences of mean values for firing

[9] Usually, the first five discharges recorded after isolation of the unit were selected for measurement to minimize effects of injury and deterioration.

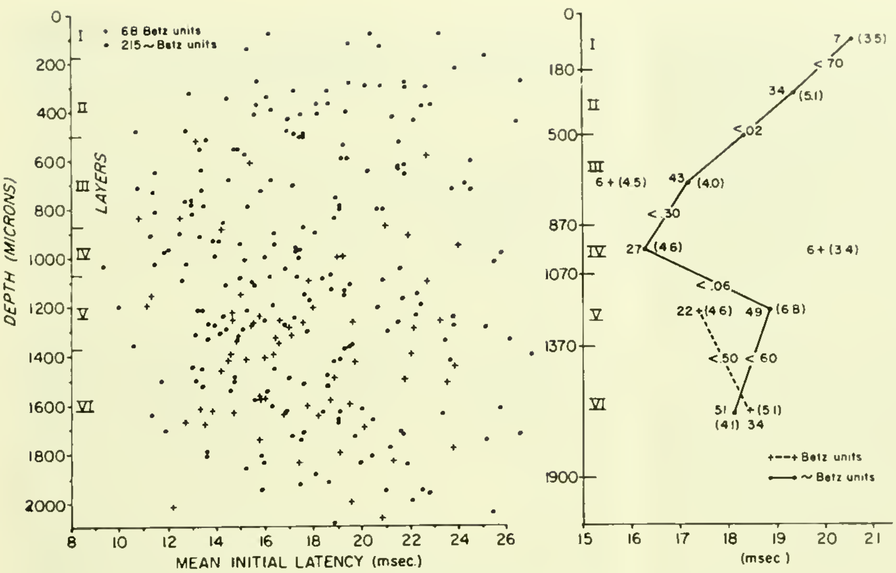

FIG. 16. *Left.* Graph showing initial spike latency of cortical cells isolated at different depths from the surface of cortex in chloralose-anesthetized cats. *Roman numerals on the ordinate* also show average extents of cytoarchitectural layers. All cells isolated in arm area I and fired by shock to contralateral footpad. Betz cells denoted by *crosses*; other cells by *dots*. *Right.* Mean initial latencies of units isolated in different cytoarchitectural layers. *Numbers* to the *left of points* indicate number of units; *bracketed figures* to the *right*, standard deviations of the means. *Numbers between points* give probability that the null hypothesis is correct. (From Patton & Towe, unpublished observations.)

latencies of Betz cells in the different layers may reflect synaptic spread downward from layers III and IV, but the differences are too small and the variation too great to permit the drawing of definite conclusions.

BETZ CELL SPIKE

Another means of investigating the excitation of Betz cells is intracellular recording of spike potentials, a method of proved value in similar studies on spinal motoneurons. Unfortunately, the application of this useful technique to cortical cells is much more difficult than experience with spinal motoneurons would suggest (4, 66, 97). Despite repeated attempts, the authors have succeeded only rarely in obtaining satisfactory intracellular recordings from cortical neurons. Cortical movements due to respiration and pulse, even when reduced to a minimum by pneumothorax, cisternal drainage and the use of a plate pressed on the cortex (3), are serious handicaps. In addition, cortical cells appear to be more fragile than their spinal cousins, and penetration (indicated by d.c. shift) is usually accompanied by the familiar, agonizing, injury squeal followed by dismal silence. That movement is only partly responsible is suggested by the fact that extracellular spikes of amplitudes (10 to 20 mv) compatible with close proximity of the electrode and the cell membrane may be recorded for an hour or more without deterioration or indication of injury.

To Phillips (85) goes the credit for obtaining the first significant series of intracellular recordings from Betz cells. In 69 experiments on cats anesthetized with hexobarbitone, he successfully penetrated 16 Betz cells maintained in an excitable state for periods of 5 to 40 min. Membrane potentials ranged from 48 to 69 mv; spike amplitudes (antidromically evoked by pyramidal stimulation), from 45 to 84 mv, with overshoots ranging from -17 to $+20$ mv. The antidromic spike often displayed an inflection on the rising phase, suggesting delayed conduction over regions of low safety factor similar to that observed in motoneurons (15). In extracellular recordings, Patton & Towe (unpublished observations) observed inflection points on the descending limb of positive-negative spikes. These inflections sometimes split off into pure positive deflections of reduced amplitude during high-frequency antidromic stimulation. The most probable point for such blockage is the axon-soma junction (23), but conduction through this region seems to be less tenuous in Betz cells than in motoneurons because in

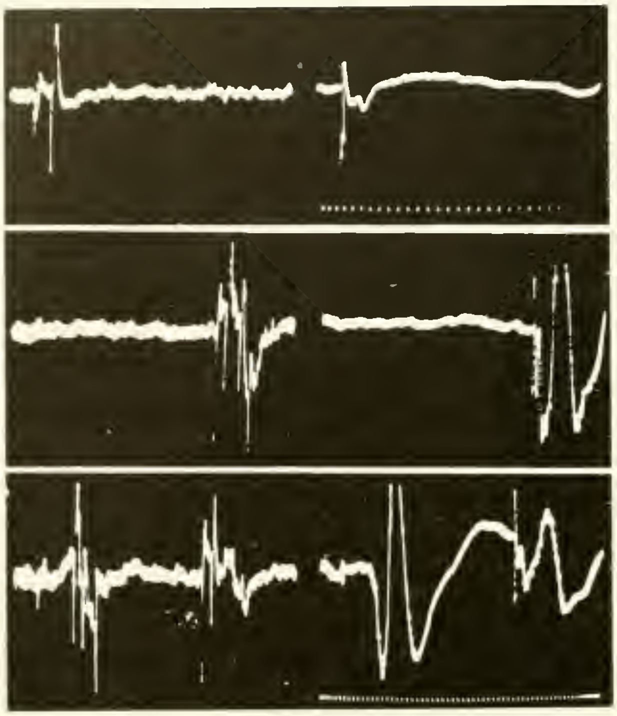

FIG. 17. Response of Betz cells to threshold and suprathreshold antidromic pyramidal shocks in cats under chloralose-decamethonium anesthesia. *Left column*, unit responses; *right column*, surface responses (area I). *Upper*. Response to threshold stimulus (0.01 msec. pulse) to bulbar pyramid; single spike on left followed repetition rates of 100 per sec. (not shown). *Middle*. Responses to suprathreshold (0.04 msec. pulse) pyramidal shock; only first of three spikes in *left figure* followed 100 per sec. stimulus rates (not shown). *Lower*. Shock to contralateral forepaw precedes suprathreshold pyramidal shock; note in test responses that late spikes are blocked and late surface deflection attenuated. Time, 2 msec. (From Patton & Towe, unpublished observations.)

many units splitting cannot be demonstrated even with stimulation rates up to 200 to 300 per sec. Phillips observed the inflection in 7 of 16 cells.

Unfortunately, Phillips did not study orthodromic excitation of Betz cells, but his figure 4 shows spikes elicited in a unit (not a Betz cell) by a strong shock to the pyramid which clearly exerted its effect by spread to the medial lemniscus. The spike arises from a slowly developing prepotential similar to that observed in intracellular recordings from orthodromically excited motoneurons (see also 4, fig. 1). Also, in spontaneously arising trains, spikes were preceded by slow depolarization which was abolished by the spike only to build up again to the firing level which varied only within narrow limits.

Following a spike (antidromic or spontaneous), the membrane potential often showed an increase which decayed over a period of about 50 msec. Phillips ascribed this postspike hyperpolarization to inhibitory action of recurrent axon collaterals, comparable to that described for spinal motoneurons (32); but on the basis of evidence discussed below, this explanation must be rejected. It is more probable that the postspike hyperpolarization is comparable to that described in the lightly stretched stretch receptor of crustaceans (34) where there are no recurrent collaterals. In the latter instance, hyperpolarization (relative to the prespike membrane potential) results when the antidromic spike invades the slowly conducting dendrites. The depolarizing effect of the dendritic generator potential on cell body membrane potential is probably reduced either because the potassium permeability of the cell body is increased during recovery or because the generator potential is temporarily obliterated after the spike invades the generator region. Similar postspike hyperpolarization has been described in other excitable structures in which membrane potential was reduced prior to firing. In Phillips' experiments on lightly anesthetized animals, some depolarization of cells was suggested by the spontaneous firing and by membrane potentials lower than expected for 'resting' neurons. That the apical dendrites of Betz cells, like the dendritic terminals of crustacean stretch receptors (33, 34, 48), are sites of nonpropagated generator potentials which bias the excitability of the cell body (23) remains to be proved, but has been ably and convincingly argued by Clare & Bishop whose papers (28, 29) may be consulted for summary and references.

Extracellularly recorded spikes of Betz cells (figs. 13, 17, 18) do not differ significantly from similarly recorded spikes of other cortical cells (3, 66, 67); they are usually positive-negative, occasionally negative. Antidromic spikes are often indistinguishable from orthodromically elicited spikes, but occasionally there are minor differences, as in figure 18 in which the antidromic spikes are consistently of greater amplitude than the orthodromic.

RECURRENT AXON COLLATERALS OF BETZ CELLS

The axons of Betz cells give off a profusion of collateral branches within the gray matter (23, 74, 88). Axon collaterals of cells in the internal lamina not only ramify within layers V and VI but course upward to branch among the cells of layers III, II and even I. Layer IV apparently receives few axon col-

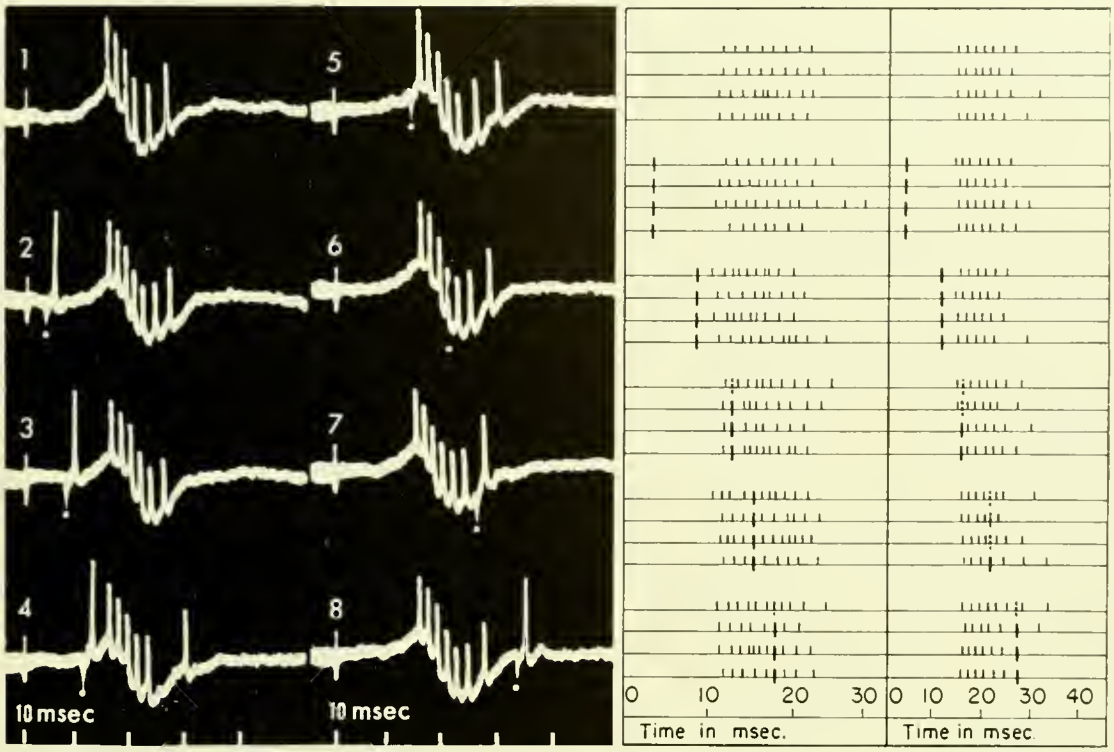

FIG. 18. Interaction of antidromically and orthodromically evoked spike activity of Betz cells in cats anesthetized with chloralose. *Left. 1*, response of Betz cell in somatosensory area I to shock to contralateral forepaw; *2–8*, responses to threshold pyramidal shocks and contralateral forepaw shocks delivered at different time intervals. Pyramidal shock artifact marked by *white dot* under traces. *Right.* Diagram of similar data from two Betz cells showing four samples for each conditioning-testing interval. *Heavy line*, antidromic spike; *dotted line*, expected position of blocked antidromic spike; *light line*, orthodromic spike. (From Patton & Towe, unpublished observations.)

laterals from neurons of other layers. The prominence of the collateral system has led to some investigation and considerable speculation concerning its function. Chang (25) deduced, from analysis of antidromic potentials recorded from the cortical surface in rabbits, that the collaterals are capable of re-exciting Betz cells to produce repetitive discharge. Patton & Towe (unpublished observations) have been unable to confirm this in cats (fig. 17). The response of Betz cells to a threshold antidromic pyramidal shock was invariably a single spike of short latency and was capable of following high rates (100 to 200 per sec.) of repetitive stimulation. With stronger stimulation, one or more late spikes followed the early spike, and a positive deflection of about 3 msec. latency was grafted onto the surface cortical response. The late positive surface wave was greatly attenuated, and the late spikes failed at stimulus rates of 20 per sec. Moreover, both the late spikes and the late positive wave were blocked by an antecedent shock to the contralateral footpad (fig. 17). It thus seems likely that repetitive firing to antidromic shocks occurs only when the stimulus spreads to the lemniscus.

Nor do the recurrent collaterals cause detectable inhibition, as suggested by Phillips (85, 86) and Purpura & Grundfest (87). Figure 18 shows experiments in which antidromic and orthodromic volleys were delivered to the cortex in combination and at various conditioning-testing intervals. In no instance was antidromic invasion followed by depressed excitability beyond that expected from refractoriness. The function of recurrent axon collaterals of Betz cells remains problematical.

PYRAMIDAL FIBER SIZES AND CONDUCTION VELOCITIES

In all species the pyramidal axons are characterized by their fineness (20, 60); in man, only 61 per cent are myelinated and of these, about 90 per cent are of

A delta, or Group III, size (less than 4 μ in diameter). Only 1.75 per cent of the myelinated fibers are in the group I diameter range (11–22 μ).

Conduction velocities of pyramidal tract fibers were first determined by Lloyd (72) in a study which is noteworthy because it is one of the few in which strict attention was given to eliminating extrapyramidal fibers; recordings were made in the lateral column of the cord of decerebrate cats following stimulation of the bulbar pyramid above a section transecting all of the bulb but the pyramids. Maximal conduction velocities were 60 to 65 m per sec., and although minimal velocities were uncertain, elements conducting at rates as low as 18 m per sec. were detected. Brookhart & Morris (20) observed two components in the antidromic complex recorded in the bulbar pyramids following shocks to the lateral column of the cord, one conducting at maximal rates of 100 to 160 m per sec. and the other at 45 to 55 m per sec. It seems likely that the rapidly-conducting component represents activity in other (perhaps reticulospinal) systems. In one monkey, Patton & Amassian (80) recorded D waves conducted over 14 cm from cervical to lumbar cord at 52 m per sec. Bernhard *et al.* (10) found maximal velocities of 60 to 70 m per sec. in the monkey. These values are consistent with the anatomically determined fiber spectrum of the pyramid.

Conduction velocities computed for the cortex-to-bulb portion of the pyramid are often higher than those found for the bulb-to-cord portion. Thus, Woolsey & Chang (112) estimated that antidromic impulses traversed the distance from bulb to cortex at speeds ranging from 100 down to 1.8 m per sec. Patton & Amassian (80) sometimes found D-wave conduction times from cortex to bulb suggesting maximal velocities up to 80 to 100 m per sec. Bertrand (12) found D-wave velocities of 89 m per sec. from supplementary motor cortex to cervical cord. It is uncertain whether the high computed velocities in these experiments result from inaccurate estimation of conduction distance, or whether they reflect the true mean velocity of the upper corticospinal fibers before they have become attenuated in diameter by collateral branching in the pons and midbrain. Single unit recording of antidromic spikes in Betz cells give values closer to those found for the bulb-to-cord portion of the tract. Patton & Towe (unpublished observations) found units conducting from 64.0 to 5.6 m per sec. (assuming conduction distance of 43 mm), and Phillips (85), using intracellular recording which probably preferentially selects large cells with large axons, found values from 78 to 18 m per sec.

Bishop *et al.* (13) recorded from the surface of the pyramid a bimodal compound action potential following a shock to the pyramid at the level of the trapezoid body. We have confirmed their findings; in our experiments, the two deflections have velocities of 59 m per sec. and 14 m per sec., and clearly represent two fiber groups, for their refractory periods are independent of one another and the threshold for the fast group is lower than that for the slow group. Whether both groups traverse the pyramids is not clear. According to Bishop and his co-workers, the excised pyramidal tract shows a similar compound action potential, but it may be questioned whether pyramidal fibers can truly be separated from lemniscal and other fibers by this procedure. Following contralateral pyramidal stimulation, both waves may be recorded from the lateral surface of the cord as far down as the third lumbar segment, and cord responses are abolished by pyramidal section below the point of stimulation (49).

AFFERENT FIBERS IN PYRAMIDS

The bulbar pyramid has long been considered a purely descending bundle. This view is challenged by Brodal & Walberg (17) who saw degeneration in the pyramid (prepared with Marchi and Glees silver stains) following lesions of the lateral or ventral spinal cord and in the dorsal column nuclei of cats. Some of the ascending fibers are said to arise from cord segments as far caudal as the fifth lumbar segment (but mostly from cervical segments) and to join the pyramids at the decussation where some cross and others continue on the same side through the bulbar pyramids, the peduncles, and the internal capsule to the sensory and motor area of the cortex. A greater number of fibers are said to arise from the dorsal column nuclei (particularly the cuneate nucleus) and to follow a course similar to that of the fibers arising from spinal segments. Both groups of fibers give off collaterals to the pontine nuclei. A similar system of ascending fibers has been described in the pyramid of man (78). The numbers of ascending fibers are small (only about 4 per cent of the total pyramidal population). Perhaps this accounts for the fact that no clear-cut evidence of their presence can be found by electrical recording methods. The afferent activity recorded by Brodal & Kaada (16), and ascribed by them to ascending fibers in the pyramid, is clearly ascribable to volume pickup from the medial lemniscus (see figs. 19, 20), as can be shown by careful histological verification of recording sites and differential recordings (54, 82).

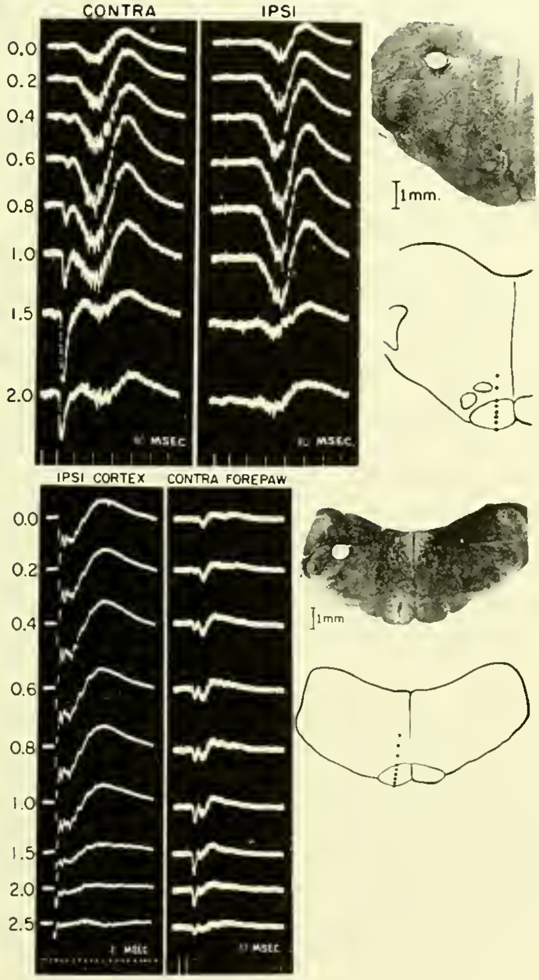

FIG. 19. Bulbar responses to forepaw and cortical stimulation in cats anesthetized with chloralose. *Upper.* Responses to contralateral and ipsilateral forepaw stimulation recorded at the points indicated in the drawing. Depth from surface of pyramid indicated by *numbers* at *left.* Note different locations for maximal recording of afferent wave and corticofugal wave. *Lower. Left column* shows D-I complexes evoked by stimulating the ipsilateral area I; *right column,* responses to contralateral forepaw stimulation. Depths indicated by numbers. Note different locations for maximal recording of afferent wave and D-I complex (corticofugal wave is small because of cortical exposure).

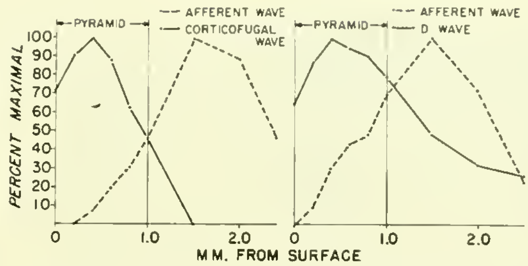

FIG. 20. Graphic representation of data from fig. 19. *Ordinate,* size of response; *abscissa,* depth of recording electrode in millimeters from the pyramidal surface.

TOPOGRAPHICAL ORGANIZATION AND COURSE OF PYRAMIDAL TRACT

It has been pointed out previously that the cortical origins of the pyramidal fibers destined for the cervical and lumbar spinal segments are recognizably distinct (although overlapping at the borders) and correspond to the classical arm and leg motor subdivisions as determined by mapping foci for movement.[10] Indeed, such mapping experiments indicate an overlapping mosaic of cortical foci controlling individual muscles (26). Unfortunately, the attractive and likely hypothesis that pyramidal origins are similarly discretely localized cannot be tested by experiments in which both pyramidal and extrapyramidal origins are excited.

To what extent is the cortically established separation of arm and leg pyramidal fibers maintained in the descending course of the tract? According to Barnard & Woolsey (6), who traced Marchi degeneration in monkeys following carefully controlled discrete cortical lesions, some degree of topographical organization is seen in the internal capsule but with considerable overlap. Leg fibers are situated most caudally in the posterior limb of the capsule, with fibers for distal arm and proximal arm located more rostrally in that order. At the midbrain and pontine levels, the separation becomes less distinct; and at the bulbar and spinal levels, fibers destined for the arm and leg segments are thoroughly mixed. Both Tower (103) and Mettler & Mettler (77) observed that deficits resulting from partial pyramidal lesions were equally prominent in forelimb and hindlimb.

[10] This fact has been questioned by Glees & Cole (40) on the basis of finding 17 degenerated fibers (Marchi stain) in the lumbar lateral column of monkey following a cortical lesion said to be restricted to the arm and face motor divisions. Even discounting the capriciousness of the method and the opportunity for injury to cortical regions other than those intentionally ablated, this finding appears an inadequate challenge to the doctrine of topographical organization; no one seriously questions some overlap of cortical topographical regions. That pyramidal fibers destined for lower cord segments do not give off a significant number of excitatory collaterals in the cervical region was first shown by Fröhlich & Sherrington (36) who noticed that antidromic corticospinal stimulation in the oral end of the severed thoracic cord produced no forelimb movement.

The course of the pyramidal tract in the spinal cord has been traced repeatedly with degeneration techniques (6, 27, 39, 40, 44–46, 60, 65, 89, 90, 93, 96). The major bundle is crossed and occupies the lateral column, but a variable number of uncrossed fibers in the lateral and ventral columns have been described. D waves following stimulation of the precentral gyrus in monkey are recorded only in the contralateral lateral column. (Surface electrodes on either side of the cord record a triphasic deflection larger on the contralateral than on the ipsilateral side. That the ipsilateral recording results from volume pickup from the opposite side is indicated by the fact that penetration converts the contralateral response to a pure positive deflection, but the ipsilateral responses remain triphasic regardless of depth of recording.) Bertrand (12) found prominent ipsilateral responses following stimulation of the supplementary motor area.

The spinal extent of the tract is variable in different species; in the cat, monkey and man, it reaches the lumbar segments. However, the distribution to different segments is unequal; in man, 50 per cent of the fibers terminate in the cervical region, 20 per cent in the thoracic and 30 per cent in the lumbrosacral segments (107). Uncrossed fibers appear to be destined largely for cervical segments.

SPINAL MECHANISM OF PYRAMIDAL TRACT

The connection between pyramidal tract fibers and motoneurons in the spinal cord has been investigated repeatedly with a variety of anatomical techniques. In the cat it appears that no fibers terminate directly on anterior horn cells.[11] After lesions of the sigmoid, the coronal or the anterior ectosylvian gyri, preterminal degeneration was found largely in the base of the contralateral dorsal horn with a few degenerating terminals in the intermediate gray. No degeneration was found in the ventral horn.

These anatomical findings are amply confirmed by electrophysiological studies. Lloyd (72) found that a volley initiated in the cat bulbar pyramid (after section of other descending and ascending tracts) reached the lumbar cord after about 4.5 msec. and because of temporal dispersion, persisted for 10 msec. or more. The earliest postsynaptic activity was in the external basilar region and occurred very shortly after arrival of the pyramidal volley, although exact measurements were made impossible by the prolonged asynchronous discharge of the pyramidal collaterals which intermingle with the external basilar interneurons. A single pyramidal volley is capable of eliciting a discharge in these elements lasting 20 to 30 msec.; whereas four shocks at brief intervals increase the discharge duration to some 40 msec. It thus appears that the cells of the external basilar region constitute the major direct target of pyramidal endings.

Cells in two other regions of the cord fire only later; these are the solitary cells of the dorsal horn (latency, 9 to 10 msec.) and the cells of the intermediate gray substance (latency, 12 to 20 msec.). Neither of these groups responds to single pyramidal volleys but requires usually three or more before beginning to discharge. It seems likely that most of the presynaptic drive to these elements is relayed through the external basilar interneurons, although the possibility of sparse direct connections with pyramidal endings cannot be excluded.

The influence of pyramidal volleys on motoneurons is most conveniently studied by measuring the facilitation of segmental monosynaptic discharges following pyramidal conditioning. Such facilitation is detectable only after three or more pyramidal volleys, delivered at brief intervals, and has a latency of 12 to 20 msec. measured from the first pyramidal shock. Since motoneuron facilitation closely parallels in time the discharge of interneurons in the intermediate gray substance, it seems probable that the two events are causally related and that most pyramidal impulses are relayed through external basilar and intermediate interneurons before reaching the motoneuron. This conclusion is further supported by the fact that pyramidal volleys regularly facilitate three-neuron-arc discharges (which can be facilitated at the interneuronal as well as at the motoneuronal level) some 3 msec. earlier than the monosynaptic discharge (which, of course, can be facilitated only at the motoneuronal level). The sequence of events can thus be summarized as follows. The pyramidal volley reaches the lumbar cord about 4.5 msec. after bulbar pyramidal stimulation. External basilar cell discharge apparently requires a summation period of about 4.5 msec. since facilitation of trisynaptic arcs is not detected until 9 msec. after conditioning. After a summation time of another 3.0 msec., solitary cells and intermediate neurons begin to discharge, leading to motoneuronal facilitation at about 12.0 msec. The relationships are shown diagrammatically in figure 21.

[11] The authors are indebted to W. W. Chambers and C. N. Liu for permission to use material from a manuscript in preparation describing studies with Nauta stain of degeneration in the cat spinal cord following cortical lesions.

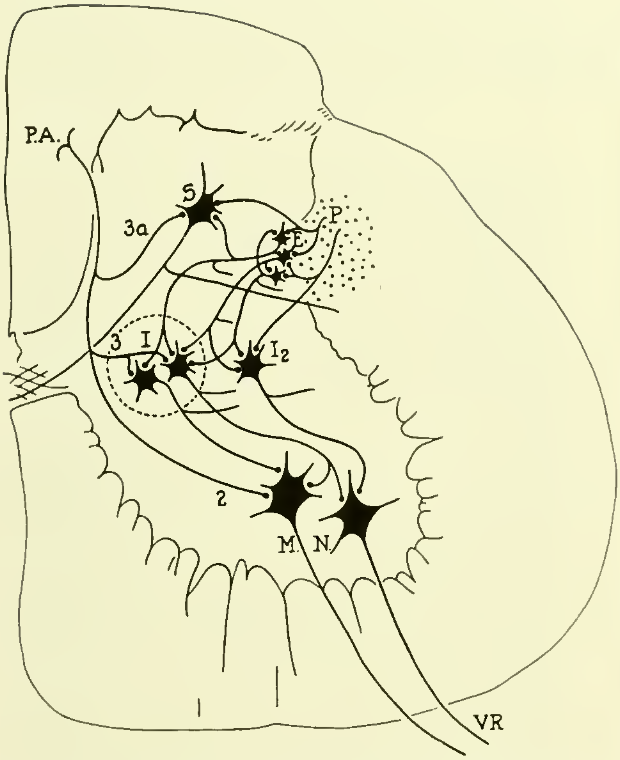

FIG. 21. Diagram of spinal connections of pyramidal tract fibers in the cat. *E*, small cells of the external basilar region; *I*, intermediate gray nucleus of Ramón y Cajal; I_2, other neurons of the intermediate region; *M.N.*, motoneurons; *P*, pyramidal tract; *P.A.*, primary afferent collaterals; *S*, solitary cells of the dorsal horn; *VR.*, ventral root; *2*, *3*, and *3a*, terminal collaterals of the primary afferent system. [From Lloyd (72).]

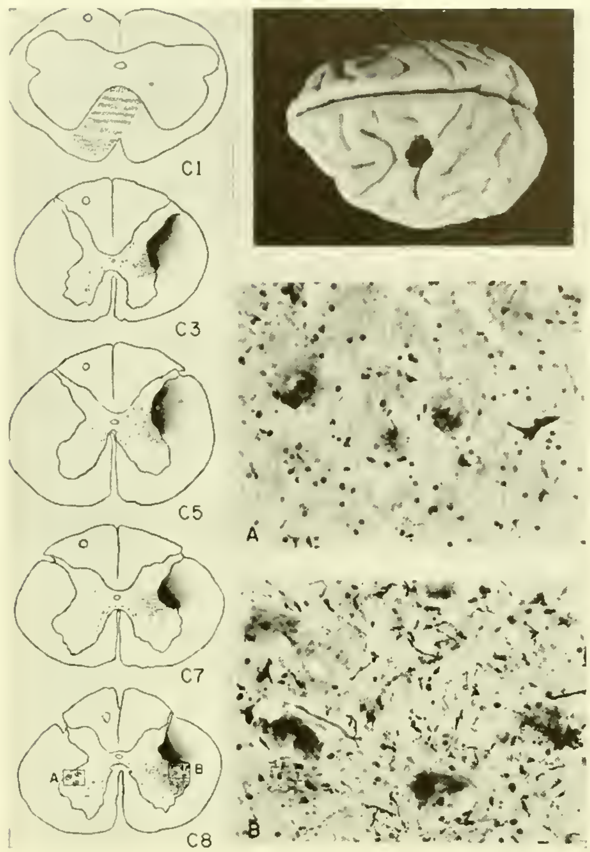

FIG. 22. Degeneration in cervical spinal cord of monkey following lesion of arm motor area. Photograph at *upper right* shows lesion as revealed at autopsy 10 days after operation. *Diagrams on left* show distribution of degenerating terminals at indicated spinal levels. In lateral columns density of degeneration is indicated by density of shading. Photomicrograph of Nauta-stained section from region A in C_8 is shown in *A* on *right*. Note absence of degeneration. *B* shows a comparable section from the ventral horn contralateral to the lesion (region B in C_8). Degenerating terminals are abundant, and many appear to end on motoneurons (note cell on extreme right). (Courtesy of Orville Smith and June DeVito.)

It is of interest that, in the cat, the influence of pyramidal conditioning on motoneuronal discharge was invariably facilitatory. In a few instances inhibition of tonic discharges in interneurons was observed, but the over-all effect on ventral root discharges was facilitatory. It is likely that interneuronal inhibition reflects reciprocal innervation; to determine the effect of such reciprocal innervation of interneurons on motoneuronal excitability would require separate recordings from motor nerves supplying antagonistic muscles rather than ventral root recording which samples motoneurons without regard to peripheral destination. Such experiments have not been performed.

In the monkey, where the pyramidal tract is more highly developed than it is in the cat, there appear to be some direct connections between pyramidal axons and motoneurons. Hoff & Hoff (46) found degenerating boutons on motoneurons in monkeys surviving precentral lesions. Figure 22 shows the distribution of degeneration (as revealed by the Nauta technique) in the monkey cervical spinal cord following a lesion of the arm motor area. Degenerating terminals on and around motoneurons at C_8 are shown clearly in the photomicrograph on the lower right (*B*). In agreement with this anatomical evidence, Bernhard and others (8, 9, 11, 19) found facilitation of monosynaptic discharges occurred after arrival of a single cortically-induced pyramidal volley with a latency too brief to permit interneuronal relay. However, monosynaptic discharge of motoneurons occurred only after repetitive cortical stimulation, and during prolonged repeti-

tive stimulation displayed a curious periodic waxing and waning, the origin of which is not clear. It thus appears that monosynaptic discharge of motoneurons by pyramidal volleys occurs only on a background of facilitation provided by bombardment through more complex pathways.

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The extrapyramidal motor system

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CHAPTER CONTENTS

INTRODUCTION

Scope of Subject

A neurophysiological synopsis of the extrapyramidal motor system is difficult for several reasons. First, the

[1] The first part of this chapter (p. 864 to p. 901) was written by Professor Hassler, the second part (p. 901 to p. 922) by Professor Jung. The introduction and conclusion were also prepared by Professor Jung. The German text of Professor Hassler's portion was translated by Dr. Johannes P. Gangloff, whose great care is gratefully acknowledged by the authors.

'extrapyramidal system' was defined anatomically and, worse still, this anatomical definition was a negative one—the central motor mechanisms excluding only those of the pyramidal tract. Second, our knowledge concerning extrapyramidal functions stems mainly from neurological observations in man. The contribution of animal experiments to this field has been relatively small. Third, a 'motor system' without sensory control is a fiction, not even a useful fiction. Therefore, sensorimotor integration and dynamic interpretation must be considered here. Thus some overlap with the other chapters on the central organization of motor functions in this work will be inevitable.

Literally the 'nonpyramidal motor system' would include all motor functions that are not mediated through the pyramidal tract. The anatomical definition as a 'nonpyramidal motor system' leads to the difficulty that, as lower vertebrates have no pyramidal system, evidently their entire motor regulation would of necessity be 'extrapyramidal.' Our subject has to be narrowed down to the physiology of the basal ganglia and some general principles of their motor functions in man and in some laboratory animals. Among the functions of the basal ganglia, only motor effects and their afferent control are described. For this reason the contributions of neuroanatomy and clinical neurology have to be considered on an unusually large scale. This may be an excuse for the contribution of two neurologists, one working mainly as a neuroanatomist (R. H.), the other as a neurophysiologist (R. J.), and for the rather extensive space which neurological details occupy in this chapter.

In the following we deal only with those basal ganglia conventionally considered part of the so-called extrapyramidal motor system. We will not treat the amygdala and other rhinencephalic parts of the basal ganglia nor the thalamus, except those nuclei connected with the striatal system. The nonspecific thalamoreticular system will be only briefly mentioned insofar as auxiliary motor functions in the regulation of sleep, wakefulness and attention are concerned. The lower brain-stem mechanisms related to the vestibular system are treated in other chapters of this work.

The term 'center' is used in the following approximately in the sense of Winterstein (296) as a structure in the central nervous system without which a certain function cannot be carried out normally and, in the sense of Hess (108), as a device in the central nervous system to establish connections, dependent upon the peripheral milieu situation, the organization of which is directed towards a definite functional result. Centers need not always be anatomically circumscribed structures defined as 'nuclei' of the central nervous system. Although we try not to imply that specific motor functions can be 'localized' in certain nuclei, some correlations seem to be well established. Thus in general one may quite safely call the extrapyramidal structures centers for the integration and regulation of motor behavior.

Development of Concept of Extrapyramidal Motor System

With the exception of the cortical extrapyramidal areas and pathways, the concept of the extrapyramidal system has its origin in the findings of human pathology. The 'extrapyramidal motor system in the narrow sense' of Spatz (237) corresponds approximately to the 'striatal system' of Vogt & Vogt (266, 269) with the exception of the dentate nucleus. Systematic investigation of this system started in 1911 with the observations of Oppenheim & Vogt (204) and Wilson (294), although a particularly conspicuous disease of the striatal system, the 'status marmoratus,' had already been described by Anton in 1896 (7) who proposed that this system be regarded as comprising the structures responsible for choreoathetotic movements.

The existence of corticospinal pathways other than the pyramidal tracts was first described in 1895 by Starlinger (245, 246); in 1898 Prus (214) called them 'extrapyramidal' on the basis of other findings. These pathways run through the tegmental midbrain and can produce movements following stimulation of the motor cortex even after transection of the pyramids at the medullary level as was ascertained by Rothmann (222). In numerous experiments Vogt & Vogt (267, 268) then delimited the extrapyramidal motor areas by determining the effects of cortical stimulation before and after isolation of the stimulated areas from the primary motor cortex.

Attempts to produce symptoms of extrapyramidal diseases by means of lesions have failed until recently. More recent physiological research dealing with the extrapyramidal motor system has been based upon the findings of Hines (113–115) and Fulton (64) and his school concerning the origin of spasticity, as well as the studies of Tower (254–256) concerning the results of 'pure' pyramidal lesions, that is, lesions at the medullary level. Thus it became clear that, contrary to previous concepts, it was erroneous to consider all pyramidal fibers as coming from area 4 gamma and all extrapyramidal motor fibers as originating in the other cortical areas. It was shown that many cortico-

spinal fiber systems traversing the pyramids in the medulla originate from extrapyramidal cortical areas, whereas many efferent fibers from area 4 gamma do not appear in the medullary pyramids but go to subcortical nuclei, in particular to the striatum and pallidum. Thus every cortical motor area appears to have mixed pyramidal and extrapyramidal functions. That the pyramids contain fibers of various diameters and origins has been a well-known fact since the studies of Häggqvist (74), Lassek (157) and others. Still inadequate is our knowledge of those efferent fibers from cortical motor areas which follow routes not passing through the pyramids. However, in spite of fundamental changes in our knowledge of the pyramidal tract, we do not favor a complete abandonment of the concept—in contrast to many other authors such as Bucy (23). Since all these different fibers constitute a tight bundle at the medullary level, the pyramidal tract remains a well-defined and experimentally accessible structure. Many of the earlier concepts remain valid if restricted to the largest fibers in the pyramids, because the great majority of the large pyramidal fibers have their origin in the Betz cells of area 4 gamma.

The concept of 'striate' or 'extrapyramidal motor' mechanisms has its origin in human pathology. 'Striate' or 'extrapyramidal motor' diseases are characterized by one or more of the following: an excess of spontaneous, aimless and unintentional movements, a lack of associated and synergistic movements, a persistent increase of muscle tone but with no spastic pareses, and absence of essential changes in the reflexes (84). It was the great merit of the pathological studies of Anton (7), Vogt & Vogt (269), Alzheimer, Wilson (294), Trétiakoff (258) and many others to have shown that diseases with these signs occur as a result of lesions in the striatum (the caudate nucleus and putamen), the pallidum, the subthalamic nucleus, the red nucleus or the nucleus niger. There is general agreement that these latter subcortical structures belong to the extrapyramidal motor system in the narrow sense or to the 'striatal system.' To what extent, however, other structures and fiber systems should be included in this system, will be discussed later.

Survey of Clinical Extrapyramidal Syndromes

Clinically two major groups of extrapyramidal motor phenomena may be distinguished: the hyperkinetic-dystonic syndromes characterized by an excess of motor activity, and the hypokinetic-rigid syndrome or Parkinson's disease showing a lack of spontaneous motor manifestations. The resting tremor of the parkinsonian syndrome certainly is an involuntary movement and therefore also belongs to the amyostatic phenomena described by Kleist (150) and Herz (97). On the other hand, it is very closely related to the hypertonic syndromes, is controlled largely by anterior horn mechanisms and therefore cannot be considered as a genuine hyperkinetic phenomenon. Thus, to consider the resting tremor as an aspect of the hypokinetic-rigid syndrome is not in conflict with the classification just given.

The hyperkinetic-dystonic syndromes will now be described briefly.

a) The choreic syndrome is characterized by rapid, involuntary jerks or fragments of movements occurring at irregular intervals and unexpectedly involving any muscle group of the extremities, the trunk or the head. Both the localization and degree of violence of these movements are variable and cannot be foreseen. Each single hyperkinetic episode being of short duration, the different episodes remain separated from each other. Like all other hyperkinetic phenomena they are considerably enhanced by sensory stimuli, emotional stress or voluntary movements. Furthermore, voluntary movement is impaired by difficulties in finding correct innervation, by lack of static support and by poor coordination (asynergism). It is impossible for an affected patient to keep the same posture quietly over any considerable period of time. Frequently muscle tone is definitely decreased. The anatomical defect responsible for the choreic syndrome is a destruction involving especially the small cells in the putamen and caudate nucleus.

b) The ballistic syndrome receives its name from its violent tossing movements which always begin in proximal muscle groups, spread all over the limb and last without interruption for a long time (fig. 1). The peripheral joints are affected by much slower alternating stretching and bending movements. The face also is usually involved. The movements are so rapid, violent and unexpected that the patient often falls down or gets hurt by the wide swinging excursions. When lying down, he is rolled back and forth by the movements. The limbs can hardly be moved voluntarily as every movement initiates hyperkinetic episodes which may also be started by surprise or by emotion. Pathological reflexes and increased abdominal reflexes are seen on the hyperkinetic side. Scratching of the sole of the foot evokes a very definitely enhanced flexion reflex. Disorders of sensibility due to simultaneous lesions in the major sensory pathways or in

FIG. 1. Right-sided traumatic hemiballism. Following the order to lift both arms the affected right arm is raised with delay and overshooting. The fingers take an athetoid posture. Then suddenly there begin forceful flexion synergic movements of the right arm and right leg with closing of the fist (right ankle flexed by tenotomy). After the right arm is caught with the left, it goes in a sudden extension together with the right leg. During the ballistic movement there is forced laughing. All the movements in the 16 pictures lasted less than 2 sec. [Redrawn from motion pictures made by Hassler (84).]

FIG. 2. Athetosis of the right hand. *Left:* Maximal flexion in the wrist. *Middle:* Pressure is applied to the lower arm. *Right:* A few seconds later the flexion changes to an athetotic hyperextension of the fingers. [From Hassler (84).]

their thalamic relay nuclei are present rather frequently but are not related to the lesion of the subthalamic nucleus. In one-fifth to one-fourth of the cases, disorders of the autonomic nervous system, such as hyperhidrosis, edema, vasomotor disorders and the Bernard-Horner syndrome, were observed on the side contralateral to the lesion; they are due to injury of neighboring structures. In most of the cases hemiballism is caused by a large lesion of the contralateral subthalamic nucleus.

c) The athetoid syndrome is characterized by involuntary movements which are slower and to a greater extent affect the peripheral muscle segments of the limbs and the face. The movements are wormlike, spasmodic, repetitious and frequently lead to overextention of joints, especially of the fingers (fig. 2). The joints have a tendency to become fixed in abnormal postures. The enhancing effect of emotional influences and sensory stimuli is particularly important in this disorder. Normal expressions are always exaggerated (the 'disease of associated movements' of Lewandowsky). Voluntary movements are impaired and partially impossible. The muscles are hypotonic although the tone is exaggerated during the movements. With athetosis there are also pathological skin reflexes and exaggerated normal exteroceptive reflexes. In most cases there is a combined lesion of the striatum and the external pallidum, sometimes a progressive disease of the pallidum alone.

d) The dystonic syndrome is also called proximal athetosis because of its likeness to athetosis. Every movement or even the intention to move initiates strong contractions in muscle groups preventing the movement originally intended. These muscular spasms involve the muscles of the neck and trunk (torticollis and tortipelvis). Strange postures and slow spasmodic rotations of the trunk and limbs—torsions—are characteristic motor manifestations (fig. 3). It is amazing, however, how easily complicated habits—like riding a bicycle or playing a ball game—as well as powerful efforts are performed. The resistance of the muscles to passive movement is at times below and at times above normal. The question of the anatomical substrate is still unsettled. In most cases lesions of the putamen without involvement of the caudate nucleus and pallidum have been reported. Destruction of the part of the centrum medianum leading to the putamen has been described in one hereditary case [Vogt & Vogt (272)].

e) The myoclonic syndrome is less homogeneous. It includes disorders characterized by quick arrhythmic contractions of single muscles or muscle groups with more or less wide movements at a frequency of less than 3 per sec. and also myorhythmic disorders of the soft palate or the pharynx muscles which may persist during sleep. Myoclonic movements may occur in any muscle, frequently leaping from one muscle to the other. Voluntary movements, emotional stress and heterogeneous sensory stimuli enhance all involuntary manifestations. The anatomical substrate is a lesion in the system including the dentate nucleus, red nucleus, central tegmental tract and olives. Pathogenetically a focus of hyperexcitability seems to exist in the brain-stem reticular formation which projects both rostrally to the motor cortex and caudally to the anterior horn cells.

f) In addition, there are more complex motor disorders consisting of myoclonic manifestations or of a combined variety of such phenomena. Besides convulsive contractions in the floor of the mouth, there are various types of organic tics and many extrapyramidal motor fits. In contrast to myoclonic disorders, organic tics are arrhythmic but stereotypically repeated movements of restricted muscle groups look-

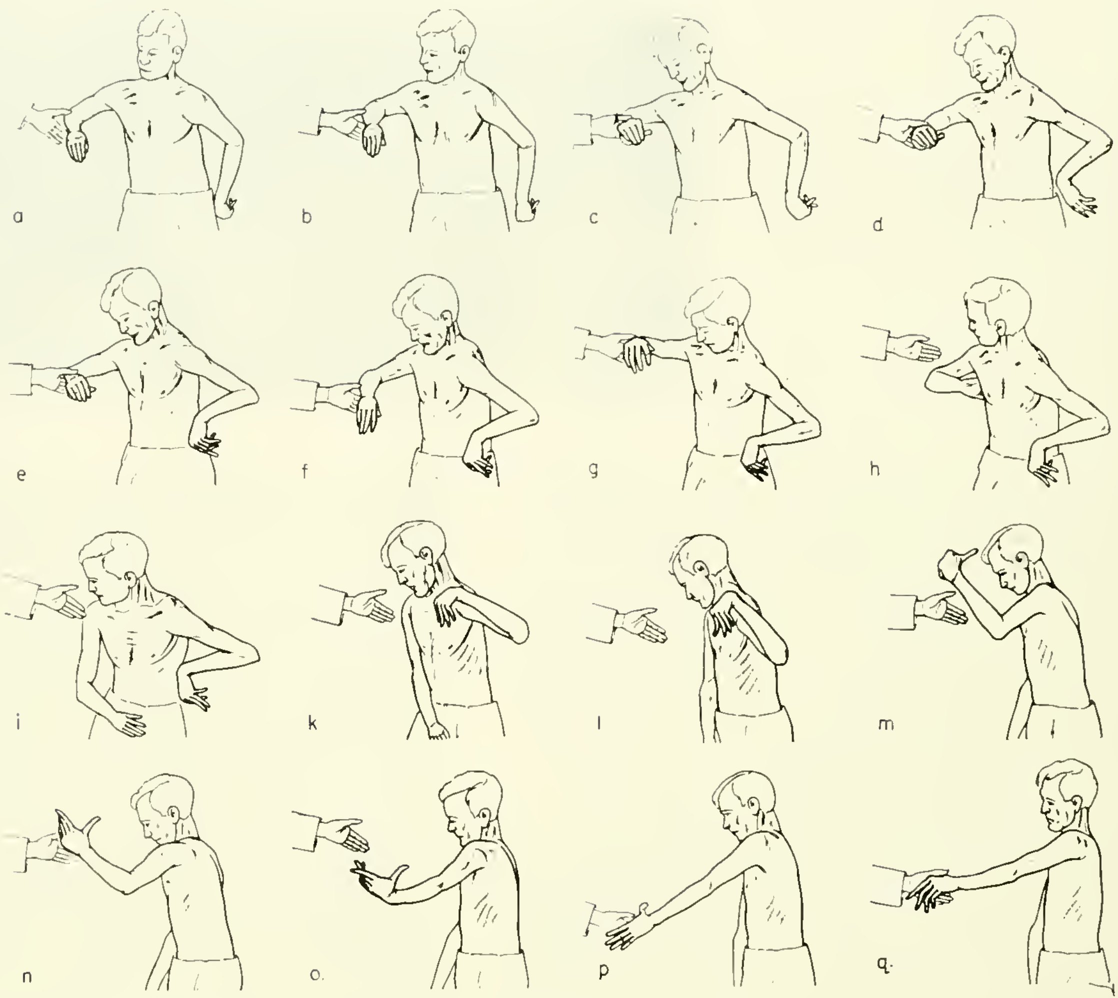

FIG. 3. Torsion dystonia during intention to reach out the left hand. The movement is retarded by spasmodic contractions of the trunk muscles and by torsion of the left arm. The fingers show athetoid movements. The dystonia is augmented during voluntary movement. [Redrawn from motion pictures made by Jung; from Hassler (84).]

ing much more like voluntary movements than do the genuine myoclonic phenomena (yawning tics, snorting tics). Even more complex stereotyped movements of the limb and speech muscles, like palilalia, are known. Lesions of the striatum are most commonly considered as the substrate for these motor disorders.

g) The hypokinetic-rigid parkinsonian syndrome differs from all hyperkinetic syndromes because of the absence of spontaneous, reactive and automatic movements. Motor stiffness, loss of congenital or acquired automatisms (akinesia) and a tenacious increase of muscle tone (rigidity) are its major characteristics. Tremor at rest, is often present although not obligatory when the patient is at rest. Impairment of voluntary activity due to the loss of automatic movements and the difficulty of initiating and performing movements may be even more pronounced than in many hyperkinetic disorders. Rigidity is not accompanied by irradiation and enhancement of the phasic stretch reflexes. Voluntary movements inhibit the resting tremor. Autonomic symptoms such as salivation, exaggerated sweating and seborrhea adiposa are aspects of the parkinsonian syndrome. The anatomical defect is destruction of nerve cells in the substantia nigra.

ANATOMY OF EXTRAPYRAMIDAL MOTOR SYSTEM

The caudate nucleus and putamen, jointly forming the striatum [Vogt (266)], are the highest subcortical centers in the extrapyramidal motor system. They may be regarded as anatomically independent of the cortex to a great extent, since they show only sparse retrograde degeneration following cortical deafferentation or ablation, and are often extensively developed in human brains with extensive congenital cortical abnormalities.

Afferent Pathways

As shown in figure 4, the most important afferents to the putamen (*Put*) and caudate (*Cd*) arise in the centrum medianum of the thalamus [Vogt & Vogt (271)]. The larger cells in the dorsal part of the nucleus project to the caudate, and the smaller ventral cells project to the putamen. In view of the essentially complete degeneration of the centrum medianum following destruction of the caudate nucleus and putamen, this nucleus may be considered as a major afferent pathway to the striatal system. In turn, the centrum medianum receives afferents from the midbrain reticular formation, according to electrophysiological studies [Starzl *et al.* (247)] and human anatomical findings [Hassler (87)]. Further afferent pathways reach the centrum medianum through the superior cerebellar peduncle [Uemura (259)]. Our own findings in man [Hassler (83)] suggest that this pathway originates in the nucleus emboliformis which receives afferents from the 'intermediate part' (Hayashi) of the cerebellum. This specifically cerebellar afferent pathway to the centrum medianum, projecting in turn to the striatum, may be of special significance in view of the integrative role of efferent cerebellar impulses in most higher motor activities. Such a role in extrapyramidal mechanisms is no longer generally attributed to efferents from the dentate nucleus.

Cortical afferent pathways to the putamen originate in the precentral motor cortex, probably chiefly in area 6, and afferents may reach the caudate nucleus from the so-called area 4s [the strip region of Hines (113)]. Brockhaus (15) has described a medial zone, the fundus striati, lying in front of the putamen and medial to the caudate nucleus and receiving afferents from the parafascicular thalamic nucleus [Hassler (81), Simma (234)].

Efferent Pathways

There are three major efferent systems, *viz.* the striopallidoreticular, striopallidocortical and strionigral. These will be discussed in more detail below. These three systems may converge either in the anterior gray matter or perhaps in the reticular formation.

STRIONIGRAL SYSTEM (CAUDATE PORTION). Efferent fibers from the caudate nucleus and putamen follow different routes to the substantia nigra and also terminate there in different parts. Efferents from the caudate follow the ventral surface of the internal capsule mainly to the anterior part of the substantia nigra and also to a dorsomedial cell group of the posterior part (fasciculus caudonigralis). Besides a few fibers from the tractus peduncularis transversus (Marburg) from the optic tract and some from the nucleus praestitialis [Hassler (87)], the two major paths to the anterior part of the substantia nigra appear to originate in the caudate nucleus and frontal cortex. Extensive degeneration in the anterior part of the substantia nigra following destruction of these two afferent pathways has been erroneously interpreted as indicating an ascending direction of nigral neurons [Rosegay (220)]. Myelogenetic studies and examination of cases of cortical aplasia have confirmed its independence of the cerebral cortex and the caudal direction of its projections to the contralateral side via the anterior quadrigeminal commissure, but their further course is unknown.

PUTAMINONIGRAL CONNECTIONS. Efferent fibers from the putamen traverse the pallidum and peduncle to terminate in the large-cell groups of the posterior substantia nigra. These cells also receive cortical afferents from area 6, and from postcentral, parietal and temporal fields, and they degenerate after combined lesions of the putamen and cortex. Their efferents are directed contralaterally, as described above. The medial group of small cells of the posterior substantia nigra receive afferents from the fundus striati and probably from the prefrontal cortex. Direct pallidal connections to the substantia nigra are unknown.

STRIOPALLIDORETICULAR SYSTEM. The other main efferent pathway from both the putamen and caudate nucleus goes to the external pallidum which also receives other afferents, particularly from the intralaminar nuclei and the nucleus limitans of the

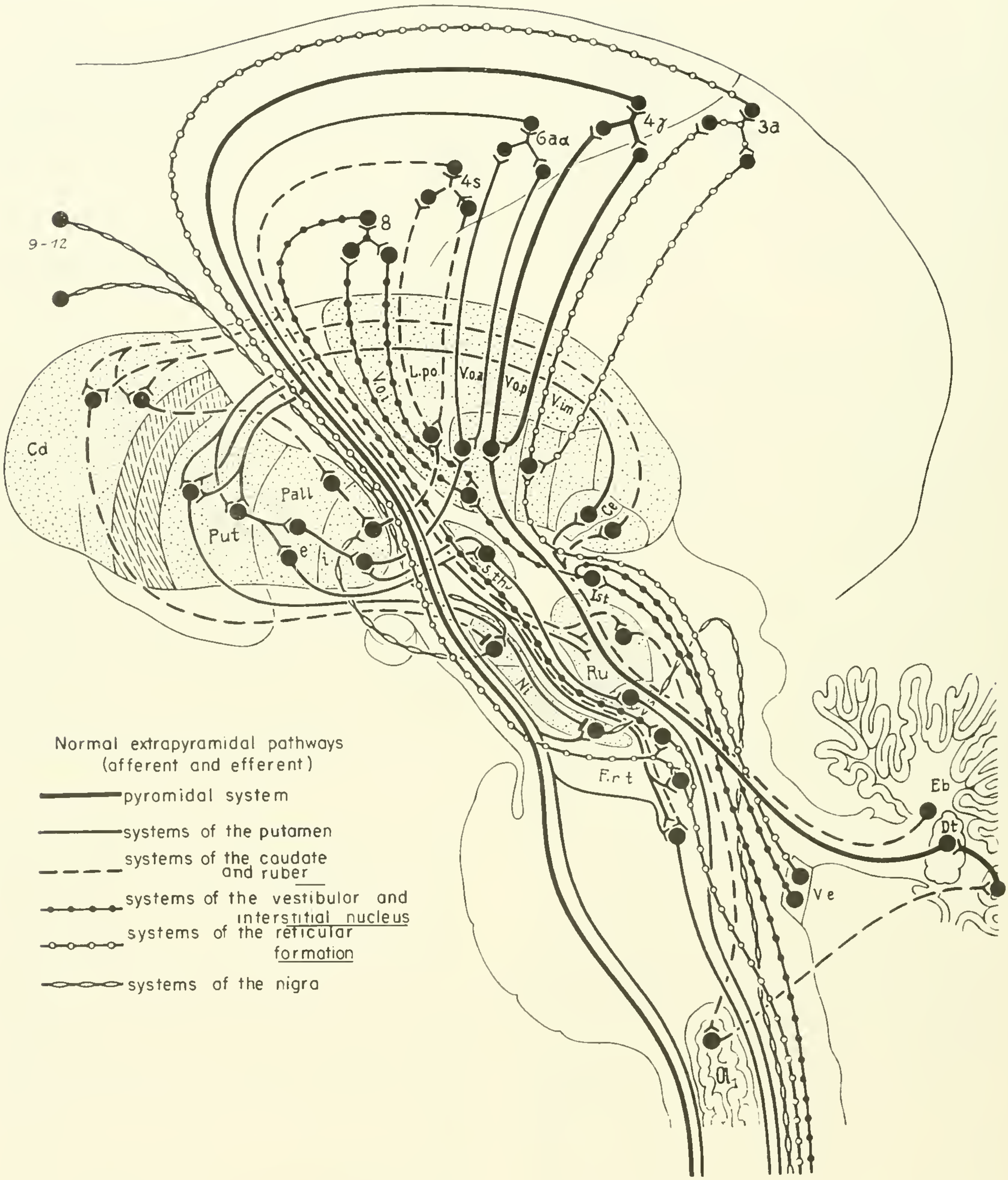

FIG. 4. Fiber connections of the extrapyramidal motor system with the afferent and efferent pathways.

Striatal systems. Afferent connections to the striatum arise from the emboliform nucleus (*Eb*) of the cerebellum, pass through centrum medianum (*Ce*) and reach both the caudatum (*Cd*) and the putamen (*Put*). The caudatum has two efferent pathways, *a*) to the nucleus niger anterior part (*Ni*) where it converges with efferent tracts from the prefrontal cortex (areas 9 to 12) and *b*) through dorsal parts of the pallidum externum (*Pall.e*) and internum (*Pall.i*) to the most rostral nucleus of

thalamus [Hassler (81)] which correspond in part to the hypnogenic zone of Hess (105) and which belong to the ascending reticular system. This forms a nonspecific projection system for all major sensory pathways. Moreover, the external pallidum receives direct connections from the medial lemniscus and the spinothalamic tracts [Hassler (81)]. An additional afferent pathway to the pallidum arises in the nucleus interstitialis Hassler (88)].

PALLIDOFUGAL PATHS. Pallidothalamocortical and descending pathways to the brain stem form the two major efferent pathways from the external pallidum. The most intimate reciprocal fiber connections exist between the external pallidum, the only equivalent of the pallidum of carnivores, and the subthalamic nucleus of Luys (*S.th.*). There is, moreover, a large afferent inflow to the subthalamic nucleus from the opposite side and from the nucleus interstitialis and praestitialis, but afferents from the brachium conjunctivum are doubtful. The possibility of cortical afferents to the subthalamic nucleus from regions rostral to area 4 is supported by studies of degeneration in human leucotomy material. Many efferent fibers from the subthalamic nucleus return to the pallidum, and particularly to its medial zones [Whittier & Mettler (293)]. Other efferent fibers descend to the midbrain as the fiber tract Q of Sano, or as the pallidosubrubral tract, and terminate in the midbrain tegmentum caudal to the red nucleus (*Ru*), according to our own observations in partial agreement with those of Papcz, Whittier and Mettler. This activity probably is conveyed further caudally by reticulospinal pathways and in part by fibers originating in the large-celled caudal portion of the red nucleus and entering the rubrospinal tract, so inconspicuous in man.

Fibers from the external pallidum also break through the internal capsule and field H2 (fasciculus lenticularis) to terminate in the ventromedial hypothalamic nucleus and in the intercalated hypothalamic nucleus. Other fibers from the external pallidum pass in the bundle H2 of Forel to the red nucleus and tegmental fiber systems.

STRIOPALLIDOCORTICAL SYSTEMS. Many of the impulses from the external pallidum are conveyed to the internal pallidum. In contrast to older concepts, the latter is not viewed as specifically an effector or motor structure, but rather, by reason of its major projections to the thalamus, as an essential link in afferent paths projecting to many cortical areas [Ranson & Ranson (217), Hassler (82)]. Most of its efferent fibers pass in the thalamic fasciculus (H1 of Forel) to terminate in the oral part (*V.o.a.*) of the nucleus ventralis lateralis of Walker, which projects

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the thalamus, the lateropolaris (*L.po*), which has two way connections with the strip region of Hines (*4s*). The efferent path of area *4s* gives collaterals to the caudatum (multineuronal feed-back path) and terminates in the red nucleus (*Ru*) and the reticular formation (*F.rt*). The putamen has two (main) efferent pathways. *a*) One goes to the nucleus niger posterior part (*Ni*), where it converges with efferent fibers from the motor cortex (areas *4γ* and *6aα*). From the nucleus niger posterior arises the nigroreticulospinal tract, and from the nucleus niger anterior the efferent fibers seem to go to the pallidum internum from which fibers to the subthalamic nucleus (*S.th*) originate. The efferent path from this nucleus reaches the pallidum internum and probably the magnocellular part of the red nucleus (*Ru*) or a subrubral region. The efferent fibers of the pallidum externum reach the red nucleus and the reticular formation. *b*) The other neuronal chain passes through the pallidum internum, the thalamic fascicle to the anterior part of the ventrooral thalamic nucleus (*V.o.a.*) which has a two-directional connection with area *6aα* of the precentral motor cortex. This area *6aα* feeds back collaterals which reach the putamen, the direct efferent path reaching the reticular formation and probably the nucleus niger and certainly the spinal cord through the pyramidal tract.

Pyramidal system. The connections of the large fiber part of the pyramidal tract originate in the parvocellular dentate nucleus (*Dt*) and reach the posterior ventro-oral nucleus (*V.o.p*) of the thalamus which has a two-directional connection with area *4γ* of the precentral motor cortex; this area is the origin of most of the largest fibers of the pyramidal tract which gives collaterals to the putamen and posterior part of the nucleus niger.

Statokinetic systems. Ascending connections of the vestibular and statokinetic systems arise in the vestibular nuclei (*Ve*) and as vestibuloreticulothalamic fibers reach the ventrointermediate (*V.im*) nucleus of the thalamus which has two-directional connections with the central region of the cortex, probably with area *3a*. This area influences by efferent fibers the part of the mesencephalic reticular formation which controls all horizontal turning movements to the same side (see fig. 17). Another path, the vestibulomesencephalic tract, runs to the interstitial nucleus (*Ist*) which coordinates rotating movements. Its efferent path, the interstitiospinal tract, reaches the cervical cord. Ascending fibers go to the inner part or ventro-oral nucleus of thalamus (*V.o.i*) which is in intimate two-directional connection with the region of area *8*, the frontal oculomotor field. Its efferent fibers influence the reticular formation; here a medial part, which controls the anterior gray column by the ventral reticulospinal tract, and a lateral part, which operates mainly through the lateral reticulospinal tract, can be distinguished. Whether the efferent mechanism of the nucleus niger is also interrupted in the reticular formation is uncertain.

Efferent systems. Efferent mechanisms are the reticulospinal tracts, the rubrospinal tract, the pyramidal tract and the central tegmental tract to the inferior olive (*Ol*) which acts as a feed-back mechanism through the cerebellum.

mainly to the precentral motor area, and especially to area 6aα in primates [Hassler (82)].

As mentioned above, the pallidum is the terminus of an important inflow from the striatum, with fibers from the caudate nucleus entering the dorsal third or fourth of the external pallidum, and projections from the putamen entering the ventral two thirds. The pallidal projections from the rostral caudate nucleus are proportionately larger from the expanded head of the nucleus. The putamen appears to exercise control mainly over the anterior part of the nucleus ventralis lateralis (nucleus ventralis oralis anterior, *V.o.a.*) previously discussed, whereas the caudate nucleus projects mainly to thalamic nuclei further rostrally, especially to the nucleus ventralis anterior (nucleus lateropolaris, *L.po.*). Although the theory of suppressor areas appears to have been refuted, it is possible that the strip region of Hines may contain a mechanism inhibiting spinal motor activity. Since Travis (257) has shown that a precentral lesion causes spasticity only if the adjacent supplementary motor area is damaged, a possible explanation of the results of experiments on the strip region may lie in concomitant damage to white matter with interruption of fiber connections to the supplementary motor area on the medial frontal surface. Thalamic projections to this area are uncertain, but may arise in nuclei dorsal to the anterior part of the nucleus ventralis oralis mentioned above. It is suggested that the supplementary motor area would receive mainly indirect afferents from the caudate nucleus via the rostral pallidum and the nucleus ventralis anterior.

The neuronal chains of the internal pallidum, the caudal chains influenced by the putamen and the rostral chains controlled by the caudate nucleus all represent important afferent pathways to clearly defined cortical fields. These cortical fields are major contributors to the pyramidal tract. Thus, this part of the extrapyramidal system becomes an afferent pathway to the pyramidal tract. The striatal system is dependent in turn on cortical fields which utilize the pyramidal tracts as efferent pathways, and in a restricted sense the pyramidal tract may be regarded as part of the mechanism of extrapyramidal activities.

RED NUCLEUS. This nucleus receives its main influx via the brachium conjunctivum from the magnocellular part of the dentate nucleus [Hassler (83)]. Since most cerebellar efferent fibers enter or traverse the red nucleus, little is known about which of the deficiency phenomena attributed to the nucleus result from damage to it and which are rather the result of interruption of fibers of passage. Fibers from the external pallidum to the red nucleus are described above. Direct vestibular afferents are doubtful. Many authors have described cortical connections, especially from Hines' suppressor strip, but their functional significance is unknown.

Two efferent pathways arise in the red nucleus. The rubrospinal tract is composed of large fast-conducting axons of the magnocellular part of the nucleus, but it is poorly developed in primates and very small in man. The central tegmental bundle leaves the dorsomedial red nucleus from the smaller cells of the nucleus and is fully developed only in primates. This bundle [the ventrolateral *Teilbündel* of Weisschedel (291)] is connected partly with the reticular formation but terminates to a greater extent in the inferior olives.

NORMAL AND PATHOLOGICAL PHYSIOLOGY OF EXTRAPYRAMIDAL STRUCTURES: EFFECTS OF STIMULATION AND ABLATION IN ANIMALS AND OF LESIONS IN MAN

Up to a few years ago the physiology of the extrapyramidal motor system was rather sterile. Many clinically established concepts could not be confirmed physiologically. In the following section it therefore appears necessary to discuss not only the results of stimulation and destruction experiments, but also the findings of human pathology.

Telencephalic Structures

STRIATUM: ANIMAL EXPERIMENTS. The results of stimulation and destruction within this highest extrapyramidal motor center have long been controversial. In spite of Ferrier's early findings (55) that faradic stimulation of the corpus striatum causes movements with pronounced bending of the head and the whole body to the contralateral side, these and the locomotor movements often observed were usually considered to be the results of stimulation of the internal capsule by escape current loops, particularly since von Bechterew (273) and Rioch & Brenner (218) could not obtain them after degeneration of the internal capsule. Wilson (295), on the basis of stereotaxic stimulation with faradic current, even considered the putamen of monkeys as unexcitable.

The first significant results were obtained with the Hess technique by means of low frequency stimulation of the caudate nucleus in unanesthetized freely moving cats. This procedure produces an apparently purpose-

FIG. 5. Contraversive turning and inactivation produced by stimulation of the caudate nucleus (intensity, 1 v., rate, 8 per sec.). *Left:* Stimulation of the left caudate nucleus near the internal capsule causes adversive movement of the head and foretrunk to the right. *Right:* Long-lasting (35 sec.) stimulation with damped d.c. impulses elicits inactivation with incompletely closed eyes and preserved muscle tone in contrast to real sleep. There is a slight contraversive turning of the head. [From Hess (109) and Akert (3).]

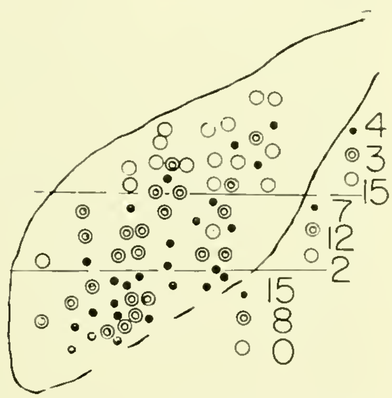

FIG. 6. Somatotopic representation of turning movements in the caudate nucleus. *Circles* represent projections onto the sagittal plane of the nucleus of points within the nucleus, stimulation of which evoked these movements: *solid circles,* head turning with or without body concavity to the opposite side; *concentric circles,* neck and trunk movements plus contralateral foreleg lifting; *open circles,* neck and trunk movements with foreleg flexion plus contralateral lifting of the hind leg. The distribution of these movements in each third of the nucleus is indicated by the *numbers* at the *right.* [From Forman & Ward (61).]

ful turning of the head and body to the contralateral side [Hassler (89)] which often becomes a circling movement to the opposite side. These movements are the result of well coordinated movements of the extremities, the trunk and the neck (fig. 5, left). Simultaneously, pupillary dilatation appears. In similar studies, Forman & Ward (61) were able to demonstrate in the head of the caudate nucleus a somatotopic localization (fig. 6). They showed that ventral areas are responsible for contraversive head turning combined with bending of the body, that intermediate areas cause contraversive movements of the neck and trunk with lifting of the forelegs, and that the dorsal areas cause the same effects with additional lifting of the contralateral hind leg. According to Hendley & Hodes (96) these contraversive turnings depend upon an intact connection between the caudate nucleus and medial parts of the nucleus niger; according to our own anatomical studies, this is also the area where direct caudonigral fibers terminate.

In further experiments Forman & Ward (61) demonstrated the independance of these turning movements of the corticospinal systems. When the motor cortex and the caudate nucleus are stimulated simultaneously in unanesthetized cats, the effect of motor cortical stimulation is not inhibited but a combination occurs between contraversive turning and movements of the extremities. Thus, it was not possible to confirm the famous results of Mettler *et al.* (184) and of Hodes *et al.* (116, 117) claiming a suppression of cortical motor effects during simultaneous faradic stimulation of the caudate nucleus. However, Forman & Ward did observe suppression of running movements as a result of stimulation of the putamen in one experiment.

A syndrome of striatal inactivation with poor spontaneous activity and a deficient motor responsiveness to external stimulation occurs after longer lasting, low frequency stimulation of the caudate nucleus. Hess (105) described these effects as partial (motor) sleep. Although the animals did not roll themselves up before going to sleep, yawning sometimes resulted from caudate nucleus stimulation. Sleep has also been found to follow caudate nucleus stimulation in monkeys and man by Heath & Hodes (94). Briefer and stronger stimulation of this structure induces arrest of all spontaneous movements, the so-called arrest reaction of Hunter & Jasper (123).

Akert & Andersson (4) have also described an inactivation syndrome evoked by caudate stimulation, as is shown in figure 5 (right), which merges into sleep.

During this inactivation, the animals show awkward paw and ankle movements and other disorders indicating disturbed proprioceptive mechanisms.

The effects of destruction of the striatum have been extensively studied. Pourfour du Petit early considered the caudate nucleus to be a ganglion essential for the control of voluntary movements. Bilateral destruction of the striatum and part of the surrounding white matter in rabbits produces an irresistible drive to run straight forward [Magendie (172), Schiff (226), Lussana & Lemoigne (171)]. The injection of corrosive liquids in the caudate nucleus also produced locomotor movements directed straight ahead regardless of obstacles (Beaumis, Fournier, Nothnagel). Nothnagel (202) realized correctly that they were complex movements and not uncoordinated contractions of single muscles. He therefore assumed that there must be a center for locomotor movements in the caudate which he called the *nodus cursorius*. After the negative results of the destruction experiments of Wilson and of von Bechterew in the putamen and caudate nucleus, these early observations were completely forgotten.

In monkeys and in chimpanzees the fact that even bilateral lesions of the anterior edge of the caudate nucleus do not cause any important disorders seems to be confirmed. Mettler & Mettler (185) were unable to find any significant impairment of motor activity in monkeys and cats with lesions in the caudate nucleus of less than 3 mm in diameter. However, when most of the caudate nucleus is destroyed, circling movements occur to the side of the lesion. After destruction of both caudate nuclei the animals show an incessant drive to walk straight ahead regardless of obstacles and in spite of a slight hypertonia of the hind legs noted by Liddell & Phillips (161). The locomotor movements of the legs are enhanced by the simultaneous absence of the frontal cortex. According to Delmas-Marsalet *et al.* (39) unilateral destruction of the caudate nucleus leads to the same disorders as does unilateral labyrinth destruction. Injection of cocaine in the ipsilateral labyrinth after unilateral extirpation of either the caudate nucleus or the prefrontal cortex enhances these circling movements, as does also passive turning in the direction of these movements. Cats with bilateral caudate destruction also seem to be disorientated and during the first postoperative days could not be influenced either by somatosensory, visual, auditory or vestibular stimulation.

The theory that these lesions exert an excitatory effect on subcortical centers must be abandoned because the locomotor movements last too long, can be triggered again by tactile or proprioceptive stimulation and can be enhanced by suppression of the visual stimuli after having ceased spontaneously 2 weeks after the operation. Akert & Andersson (4), however, describe two cats with extensive bilateral extirpation of the caudate nucleus which showed an obvious tendency to tonic spreading of the forepaws, a response which has been elicited by Hunter & Jasper (123) through stimulation of the centrum medianum. The symptoms disappeared after 3 weeks. The animals with bilateral lesions in the caudate nucleus also showed extensive changes of spontaneous motor drive and reacted like automatons following sensory stimulation.

In the macaque, Edwards & Bagg (54) observed tremor, decrease in spontaneous motor activity and occasionally postural disorders after extensive bilateral lesions of the caudate nucleus or the lenticular nuclei. As Kennard (145) was able to show in monkeys, no extrapyramidal symptoms and no tremor follow a clean bilateral lesion of the caudate nucleus, regardless of whether the operation has been performed through the corpus callosum and the ventricle or through area 8. Only if area 6 is also removed on both sides simultaneously or later does a bilateral tremor appear in addition to the typical signs of 'area 6 lesion' (namely spasticity and grasping reflex). The intensity of the tremor in these cases depended upon the size of the caudate lesion. It was not a typical resting tremor but had a frequency of 8 to 12 per sec. It appeared before and at the beginning of voluntary movements and during the assumption of certain postures of the limbs. Therefore, it is not to be regarded as a parkinsonian tremor as many investigators have done.

Bilateral stereotaxic lesions of the putamen alone or of the putamen and globus pallidus of monkeys produce tremor and spasticity only in the presence of simultaneous removal of area 6. The intensity of the tremor depends on the size of the lesion in the putamen. Simultaneous removal of area 4 abolishes the tremor as long as the paresis persists.

In monkeys a genuine chorea was never observed following lesions in the putamen or caudate. Occasionally, irregular involuntary jerks of the head and the contralateral limbs could be seen in the resting animal a few days after the operation. Only the chimpanzee with the largest bilateral lesions in both the caudate nucleus and putamen showed, contralateral to the lesion, a definite chorea which lasted one month [Kennard (145)].

There is very definite electrophysiological evidence

of a functional interrelation between the cerebral cortex and the striatum. There is a low-voltage spontaneous electrical activity both in the caudate nucleus and in the putamen. However, a high-voltage spontaneous activity develops as soon as all fiber connections with the cortex are severed. Direct stimulation of the caudate nucleus or of structures projecting to it induce slow waves of 180 to 250 msec. duration. During this time a relatively inactive phase appears in the isocortex, the hippocampus and the unspecific thalamic nuclei [Umbach (260)]. After this phase spindle activity develops both in the caudate nucleus and in the other structures. Spindle activity can also be evoked in the anterior thalamic nuclei and in the centrum medianum by delivering single shocks to the caudate nucleus. Following low frequency stimulation of the caudate nucleus the responses of the oral ventral thalamic nuclei and the centrum medianum are synchronized with the stimulus frequency. This is also true for certain areas of the frontal cortex. Stimulation of the same thalamic nuclei at higher frequency can produce a generalized desynchronization of the entire cortex [Shimamoto & Verzeano (233)].

The caudate nucleus has a high seizure threshold and a short seizure duration. Seizure activity in other structures also can be inhibited by caudate stimulation [Umbach (262)]. When the excitability of the caudate nucleus suddenly increases during a seizure in such a way that high voltage potentials develop, there is usually a simultaneous inhibition of the tonic phase followed by the onset of the clonic phase of the seizure. In animals with simultaneous lesions in the cortex and the striatum epileptic seizures and electrical seizure activity in the EEG are both particularly serious and longer lasting than in those with cortical lesions alone [Kennard & Nims (146)].

Consequently, the caudate nucleus seems to have (even more than the putamen) restraining functions controlling the level of excitability of the cerebral cortex as a whole. The lack of inhibition acutely following bilateral caudate destruction seems to be the reason for the transitory disorientation of the operated cats. This inhibitory function may play an important role under normal conditions in selectively inhibiting impulses from other sensory systems or from areas of activity which do not belong to the pattern of excitation most significant at the moment. Thus it is likely that the striatal system not only controls motor activity but also the cerebral cortex since it is a link in the unspecific projection system.

STRIATUM: STUDIES IN MAN. Atrophy of the striatum (putamen and caudate nucleus) was the first definite anatomical change observed in an extrapyramidal motor disease with a well-defined symptomatology, namely Huntington's chorea (Alzheimer, Vogt & Vogt). It has since been repeatedly confirmed that destruction of the small nerve cells of the striatum is the major lesion in this disease. This motor disorder is characterized by rapid involuntary aimless movements with irregular distribution which is enhanced by voluntary movement. Voluntary motility is severely impaired by hyperkinetic involuntary manifestations and also by a general muscular weakness and hypotonia but not by pyramidal pareses which do not belong to the picture.

However, the lesions in Huntington's chorea are not restricted to the striatal system but also occur in the grey matter of the cerebral cortex, in parts of the superior olives, in the tuberal nuclei of the hypothalamus (Wahren) and in other nuclei. There are cases with very severe chorea in spite of a very slight involvement of the cerebral cortex. Other processes, such as senile or encephalitic damage, may also cause choreiform motor disorders, as in Sydenham's chorea.

Necrosis of the putamen is characteristically accompanied by severe hyperkinetic disorders which may be choreiform or, as in Wilson's disease, may be athetotic or torsion-dystonic in character.

When perivascular foci (*état précriblé*) perforate the striatum, the only clinical sign resulting is a simple postural tremor when the patient is at rest without hypotonia, rigor or akinesis [Hassler (80)].

According to the observations in man by Narabayashi & Okuma and Cooper, the injection of procaine in the putamen may cause a transitory tremor at rest. Larger cystic foci in the base of the putamen do not produce clinical symptoms, as far as we know. More or less extensive hemorrhages involving the corpus striatum often cannot be diagnosed by their clinical manifestations. Unilateral removal of the head of the caudate nuclei had neither disadvantageous clinical effects nor therapeutic effects on parkinsonian symptoms, as the operations of Meyers (187, 188) and Browder & Kaplan (16) showed.

It may therefore be concluded that single circumscribed striatal foci of small or medium size usually do not cause clinical disorders. Disseminated damage in larger areas or large single foci cause both static tremor and tremor at rest. Severe diffuse destruction —with predilection for the small striatal cells—causes a choreiform hyperkinesia, it being assumed that

there is no participation of the pallidum or nucleus niger. The fact that it is not as yet possible to destroy the small striatal cells selectively may account for the difficulty of producing experimental chorea by means of lesions in the corpus striatum. The hyperkinetic choreic motor phenomena occasionally produced by means of lesions in the nucleus lentiformis may be due to an unintentional interruption of the strionigral fascicle in the pallidum shortly before its entry into the nucleus niger. In Huntington's chorea this fiber tract is always degenerated and replaced by glial proliferations [Vogt & Vogt (270)].

Concerning the functional significance of the corpus striatum it is not possible to draw any final conclusions because of the partial divergence between the clinical and experimental results. However, on the basis of all the data available, there is general agreement on one point, that the striatum exerts an inhibitory control on cortical voluntary motor activity. The removal of this inhibitory effect can no longer be compensated when the striatal lesion has reached a certain size; thus there appears a pathological excess of motor activity either of rhythmic or of arrhythmic character. Inhibition of cortical voluntary motor activity seems to be an essential condition for the individual to be able to concentrate temporarily on restricted sensory perceptions or specific motor performances.

PALLIDUM: ANIMAL EXPERIMENTS. The differentiation between external and internal pallidum exists only in the primates. In carnivores and rodents there is only one pallidum; the internal pallidum is clearly delimited and exists independently as the nucleus entopeduncularis. This preliminary remark is necessary because of the differing experimental results obtained in primates and in nonprimates.

Total bilateral destruction of either the pallidum or the nucleus entopeduncularis has not yet been successfully accomplished in subprimate mammals. In cats and dogs no motor effects occur following unilateral focal (but not total) destruction in the pallidum, except an occasional diminished use of the contralateral extremities. If combined with unilateral lesions of the putamen, they produce a marked hypertonus of the contralateral extremities with impairment of postural reflexes. In the macaque small lesions also have no lasting effect [Wilson (295)]. As Kennard (145) observed, monkeys with bilateral isolated stereotaxic lesions in the pallidum (without simultaneous lesions in the putamen) did not show any abnormalities of behavior. Such symptoms appeared only after additional removal of area 8 which caused an increase in spastic tonus and an action tremor. However, in all cases where larger lesions in the pallidum had been made, a definite action tremor with hypertonia was observed probably as a result of incidental damage to the internal capsule and other structures.

According to Mettler (182, 183) bilateral destruction of the pallidum without simultaneous cortical or capsular lesions produces loss of associated movements in monkeys; the animal becomes inactive and cataleptic, and retains for some time even very uncomfortable postures passively imposed upon it. Similar effects following bilateral lesions of the hypothalamus were called catalepsy by Ranson and Magoun, as was the chronic somnolence with EEG synchronization following destruction of the anterior midbrain reticular formation in the macaque and in cats [French & Magoun (63)]. They correspond to the so-called adynamic state of Hess obtained in the cat after bilateral lesions in the posterior hypothalamus and anterior midbrain, that is after destruction of the so-called dynamogenic zone. Only in monkeys [Brown (18)] and chimpanzees [Kennard (144)] do combined lesions of the striatum and pallidum produce slow worm-like nonintentional movements of the extremities.

It must be emphasized that these manifestations following lesions of the pallidum cannot properly be compared, as Lewy and others still do, with the parkinsonian syndrome in man.

Effects following experimental stimulation of the pallidum in animals will now be discussed. Stimulation of the so-called nucleus lentiformis (pallidum and putamen) produces, according to von Bechterew (273), tonic-clonic movements of the contralateral extremities and the head, even after previous destruction of the motor cortex. von Bechterew considered the pallidum as the origin of these convulsions. Wilson (295) on the other hand declared the pallidum to be electrically unexcitable. Phasic movements of the extremities, elicited by stimulation of the motor cortex, are converted into a 'state of plastic tonus' [Mettler *et al.* (184)]. The extremities are neither rigid nor is there a tremor, but they retain passively imposed postures for a long time and relax after a considerable delay.

Cortical motor responses and knee jerk reflexes can be definitely enhanced by stimulation at a rate of 100 per sec. of the posterior pallidum [Peacock & Hodes (206)]. In contrast, Hodes *et al.* (117) were able to inhibit cortical motor responses and knee jerk reflexes

by stimulating the anterior pallidum. However, some of the areas giving this effect are located within the nucleus entopeduncularis.

Following low-voltage threshold stimulation of the external pallidum with the Hess technique in cats, movements of the contralateral extremities were obtained with violent backward movements of the shoulder combined with rhythmical facial twitches [Hess (106)]. Some of the stimulated points located in the medial entopeduncular nucleus and in the internal capsule produce contraversive turning movements with transition to circling movements [Hassler (89)].

PALLIDUM: STUDIES IN MAN. The effects of pallidum stimulation in man have been studied for the first time in the course of stereotaxic operations. These findings have so far been communicated only briefly [Hassler (85, 86, 90)]. Bipolar stimulation of the internal or external pallidum with higher voltages at 20 per sec. produces arousal both in shallow and in deep anesthesia. The patient opens his eyes, tries to orient himself and shows a dilatation of the pupils. In one case of Huntington's chorea the arousal effect following stimulation of the area between external and internal pallidum was so pronounced, in spite of deep general anesthesia, that the patient became reactive to his environment and was able to say a few words; he relapsed into deep anesthesia after the end of the stimulation Repeatedly, stimulation caused respiratory inhibition and even arrest, briefly outlasting the end of the stimulation. During external pallidum stimulation the EEG shows periodical high-voltage activity which develops all over the cerebral cortex in both hemispheres. Only occasionally does it show the desynchronization typical of the electrographic arousal response in animals. Conscious patients, operated upon under local anesthesia, lose contact with their environment during pallidum stimulation and are unable to perform complex movements or to speak accurately. To and fro movements, which the patient had previously been instructed to carry out during stimulation, are discontinued or markedly slowed and become jerky as long as the stimulation lasts. Low frequency stimulation at 4 and 8 per sec. has no definite arousal effect but induces high voltage recruiting responses in the cortex (fig. 18). During stimulation most of the patients consistently showed a tendency (as the head was immobilized) to look to the contralateral side which could be overcome however by visual fixation. Some of the patients displayed anxiety and restlessness during stimulation of the internal pallidum at higher frequency or at voltages above threshold, described a constricting or hot feeling in the chest and occasionally a feeling of vital anxiety in the left chest; some of the patients even screamed anxiously as the stimulation was repeated.

When the internal pallidum is stimulated in patients with athetotic, torsion-dystonic or choreiform disorders, even single electrical shocks may sometimes trigger a hyperkinetic reaction of prolonged duration. This is not always the case. Stimulation with frequencies higher than 8 per sec. regularly activates hyperkinetic reactions if they had disappeared during the operation, or definitely enhances them if they continue during the operation. Even convulsive contractions of the muscles of the neck and of the sternocleidomastoid muscle, comparable to spasmodic torticollis, can be produced by pallidum stimulation, but only in patients showing this kind of disorder spontaneously. The resting tremor in parkinsonian patients can be both enhanced or transitorily blocked by stimulation of the pallidum. Following stimulation at higher frequency it can also be inhibited by synergic flexion of the contralateral arm.

Riechert, Hassler and Mundinger have also carried out destruction of the internal pallidum in man. In contrast to expectations, this operation, performed unilaterally in more than 180 patients with extrapyramidal disorders, does not cause parkinsonian symptoms on the contralateral side. Parkinsonism is thus not attributable to a pallidum lesion and is not a pallidum syndrome. The only detectable immediate effect of unilateral destruction of the pallidum in parkinsonism is suppression of the rigidity and reduction of the tremor. During gradual coagulation of the pallidum (especially of the internal pallidum) in unanesthetized patients it is possible to observe a gradual decrease of muscular rigidity. Tremor may be transitorily enhanced on the contralateral side during high frequency coagulation but is decreased after destruction has taken place. In various hyperkinetic diseases, such as chorea, athetosis and torsion dystonia, hyperkinetic motor activity is also reduced even during the course of the stereotaxic operation, especially by destruction of the internal pallidum.

Following almost complete unilateral destruction by coagulation of the pallidum, especially of the internal pallidum, yawning, increasing drowsiness, closing of the eyes, impairment of contact with the environment, arrest of spontaneous speaking, sleep or even an acute brief state of disorientation or amentia are observed, but later disappear. Transitory

euphoria may appear in the postoperative period, as Walker (286) also emphasized, but is also reversible. However, longer lasting changes, such as decreased self-awareness, slightly decreased critical capacity and decreased spontaneity or drive, combined with a well preserved responsiveness to external stimulation and an occasionally increased feeling of well-being, were observed following pallidum lesions. All these changes are much more pronounced after bilateral almost complete coagulation of the pallidum. Following this procedure performed in two stages, some patients first go into a confusional state with loss of orientation in time and space, with loss of capacity to identify persons and the environment and occasionally with severe hallucinations. As long as there is no complicating brain atherosclerosis and the lesions are not too large, these symptoms are also reversible and nothing remains but a slight psycho-organic syndrome. Here again, it is interesting to note that bilateral destruction of the pallidum does not produce any motor symptoms. In a few cases a slight akinesis relative to speech, respiration and swallowing movements appears. However, this also occurs in parkinsonian patients previous to the operation.

Experience with neurosurgical therapy of parkinsonism involving production of symmetrical almost complete bilateral lesions in the pallidum indicates that it may lead to such unfavorable psychological changes that most neurosurgeons think it advisable to avoid this type of operation.

The pallidum is the site of pathological changes in a number of disease entities, some of which may be briefly noted. In icterus gravis of the newborn, hypoxemic damage of the pallidum and nucleus subthalamicus causes demyelination and cell degeneration, associated clinically with exaggerated mimetic movements and motor reactions, athetotic hyperkinetic disorders of the muscles of the face, trunk and limbs, and changing distribution of muscle tone. Similar clinical manifestations appear in the Hallervorden-Spatz disease, where iron-free pigments accumulate in the pallidum and nucleus niger, and in the pure progressive pallidal atrophy of van Bogaert.

The status marmoratus [Anton (7), Vogt (266)] is the result of vascular damage of the basal ganglia, predominent in the putamen and caudate nucleus, which occurs in early infancy. Cell atrophy is regularly found in circumscribed areas in the external pallidum. Athetotic motor disorders result from these lesions.

Carbon monoxide poisoning characteristically causes symmetrical necrotic lesions of the dorsal border of the internal and external pallidum, and in the reticular zone of the substantia nigra. However, in contrast to older views, it is unlikely that these lesions result from hypoxemic injury since similarly localized damage of the pallidum can also be produced by hydrocyanic acid, barbiturates, morphine, etc. Symmetrical necrosis of the pallidum does not always lead to the parkinsonian syndrome if the patient recovers; many patients show psychic changes only.

As a result of damage to the external pallidum, the neuronal systems of the internal pallidum, the nucleus subthalamicus, nucleus ruber and reticular formation are disinhibited and out of control. Therefore the neuronal pathways going from the nucleus ventro-oralis anterior and nucleus lateropolaris of the thalamus to area $6a\alpha$ and $6a\beta$ also convey excessive impulse streams. Surgical interruption of this neuronal chain and of the fibers feeding back from the extrapyramidal cortical fields decreases the number of pathological impulses to the peripheral motor system and thus leads to the clinically observed decrease of the athetotic hyperkinesis. However, that there is also a loss of control within the directly descending pathways from the external pallidum to the reticular formation and the subthalamic nucleus after surgical interruption of the pallidothalamocortical systems is shown by the fact that after weeks or months the athetotic hyperkineses sometimes reappear.

Diencephalic Structures

NUCLEUS SUBTHALAMICUS: ANIMAL EXPERIMENTS. Stimulation of this structure in animals, in the older experiments of Karplus and Kreidl, Shinosaki, Ingram, and Ranson and Hannett, produces mydriasis and opening of the eyelids. Later Mella (180) and Waller (288) produced rhythmic locomotor movements in cats by stimulating in the vicinity of the subthalamic nucleus. The best results were obtained in an area lying medially to the nucleus subthalamicus in the field H of Forel. Only by means of the Hess technique of low frequency stimulation (8 per sec.) in unanesthetized freely moving cats was it possible to show that these locomotor movements are actually turning or circling movements toward the opposite side. These contraversive movements appear at almost threshold intensity. Mettler *et al.* (184) saw contractions of the contralateral muscles of the back following stimulation of the nucleus subthalamicus in monkeys and cats, an obvious turning to the contralateral side appearing

in restrained animals. Apparently the nucleus has not yet been stimulated in monkeys or human subjects.

It was interesting but not understandable without the results obtained by the Hess method that lesions in the same area in cats produce persistent locomotor movements in the horizontal plane (Mella, Waller) which in freely moving cats are directed toward the side of the coagulation. Thus they are mirror images of the stimulation effect. This disorder is a consequence of destruction of a tonic (contraversive) turning mechanism in one hemisphere. Rotation of the head alone to the side of stimulation can also be elicited by stimulating in the vicinity of the subthalamic nucleus. In these cases the stimulating current reached the ansa mesencephalica ascendens which carries fibers from the nucleus interstitialis [Hassler & Hess (91)]

In cats destruction of the nucleus subthalamicus together with a part of the surrounding fiber tracts produces nothing but a rhythmic locomotor turning movement to the ipsilateral side as a result of destruction of the tonically active mechanism in this hemisphere responsible for contraversive turning, according to Hassler (89).

Choreiform movements following lesions in the subthalamic nuclei were first observed in lower animals by Lafora (155) and D'Abundo (37). Since 1949 Whittier & Mettler (293) have succeeded regularly in producing a 'choreoid hyperkinesia' in the macaque by destruction of the subthalamic nucleus. For this at least 20 per cent of the nucleus must be destroyed without too extensive damage to the neighboring structures. Neither the force nor the duration of the hyperkinesia depends directly upon the percentage of tissue destroyed in the nucleus. A somatotopic organization of the subthalamic nucleus could not be demonstrated [Carpenter & Carpenter (31)]. The hyperkinetic symptoms appear as soon as the subject recovers from anesthesia but reach their maximum 2 to 3 days after the operation. They disappear during sleep and in narcosis and may last until death. Usually the contralateral hind leg is involved; less frequently the lower trunk muscles and the anterior limbs also show hyperkinetic movements. The face, neck, pharynx and tongue are not involved with the exception of a random head tremor. In most of the cases the involuntary movements occur in irregular sequences as persisting movements with varying amplitudes and durations (typical choreiform activity). Some of the monkeys show aimless and slow movements of athetoid character, a few a ballistic hyperkinesia characterized by particularly violent flinging movements. During quiet intervals voluntary movements may initiate the hyperkinetic phenomena, as may emotional stress. In many cases the motor hyperactivity is only intermittently present and normal activity is restored within a few days. In other experiments hyperkinesia is combined with a paresis.

These hyperkineses, chiefly choreiform in nature, are interpreted as a 'disorganization of pallidum activity,' the pallidum receiving afferents from the nucleus subthalamicus. The excess impulses from the pallidum are, according to the authors, conveyed to the midbrain reticular formation or the ventral tegmental area of Tsai through the pallidosubrubral fascicle.

Relative to stereotaxic therapy, it is important to know that, according to the observations of Carpenter *et al.* (33, 34), additional interruption of the lenticular fascicle (H_2) or the pallidum will suppress or very markedly decrease choreoid hyperkinesia while simultaneous lesions of the internal capsule do not have the same favorable effect. Hyperkinesia experimentally produced in macaques can also be reduced by other procedures: *a*) bilateral lesions in the lenticular fascicle; *b*) destruction of more than 8 per cent of the internal pallidum which, however, produces serious disorders (anorexia, somnolence and very much reduced spontaneous motor activity) leading to death within a few days. Normally, unilateral lesions of the internal pallidum do not produce these disorders but still have an excellent effect on the contralateral hyperkinesia. Larger lesions even seem to abolish hyperkinesia completely. Transection of the rubrospinal tract and bilateral destruction of nucleus cuneatus and gracilis had no effect [Orioli & Mettler (205)]. Resection of area 6 contralateral to the experimental hyperkinesia did not reduce hyperkinetic activity. Lesions of the borders of area 4 caused both a slight paresis and a decrease in strength of the hyperkinesia. However, if both area 4 and 6 were removed, as was done in a rhesus monkey, hyperkinetic activity disappeared on the contralateral side and was replaced by a nonhypertonic paresis [Carpenter & Mettler (32)]. Lesions of the internal capsule in the neighborhood of the subthalamic nucleus do not seem to affect the hyperkinesia, even if they cause pareses.

NUCLEUS SUBTHALAMICUS: HUMAN STUDIES. Destruction of this nucleus in man is followed by contralateral hemiballism, provided the neighboring structures remain relatively uninjured [Fischer (56), Jakob (129), von Sántha (281)]. This, the most violent type

of involuntary motor activity in man, has been described in a previous section (p. 865). In an extensive survey of the literature Whittier found lesions to be reported in the contralateral nucleus subthalamicus in 40 out of 56 cases of hemiballism which came to necropsy. The remaining 16 cases had lesions mostly in the striatum or pallidum, that is in a structure having a two-way connection with the subthalamic nucleus.

According to experiments in animals and to more recent therapeutic observations in man, hemiballistic symptoms do not necessarily appear even in the presence of severe focalized lesions in the subthalamic nucleus as long as there is serious damage to other neighboring structures, such as the fasciculus lenticularis (H_2) and thalamicus (H_1), the pedunculus cerebri, the internal capsule or the internal pallidum.

On the basis of these observations, Bucy & Case (24) extensively removed the contralateral arm region in the precentral cortex of a patient with monoballism of an arm and obtained disappearance of the movements; however, after a year slight involuntary movements reappeared whenever the patient thought he was observed. Later Meyers *et al.* (190) severed the white matter between area 4 and area 6aα with a beneficial and permanent effect in a case of hemiballism, as did Walker (285) in another case following transection of the medial two quarters of the pedunculus cerebri.

Bipolar stimulation at 8 per sec. of the oral ventral thalamic nucleus reproduced ballistic hyperkinesia in the contralateral arm which had disappeared during slight anesthesia, according to Hassler, Riechert and Mundinger. Even extensive therapeutic coagulation of the internal pallidum or the oral ventral nuclei did not reliably relieve hemiballism. Therefore lesions were made both in the pallidum and in the medial and posterior parts of the internal capsule close to the pyramidal tract in a region where bipolar stimulation with a current of very low intensity elicited quick twitches in the contralateral facial muscles and in the limbs at the frequency of the stimulus. Contralateral spasms like those of a Jacksonian seizure appeared during coagulation. The very definite decrease or suppression of the ballistic motor activity following the additional coagulation of the efferent pathways of the extrapyramidal cortical fields seems to be a durable therapeutic effect.

The efferent mechanisms of ballistic hyperkinesia are not known at present, as the efferent pathway of the subthalamic nucleus has not yet been definitely located. Since this path is likely to end in the neighborhood of the large cells of the nucleus ruber, release of this system reaching the anterior horn grey via fibers of the rubrospinal tract now seems probable. In man the large cells of the nucleus ruber, sending their axons through the rubrospinal tract, appear to convey impulses chiefly to the trunk and the proximal limb muscles. This could explain the onset of the hemiballistic movements in proximal parts. Furthermore, impulses to the internal pallidum are also suppressed after destruction of the subthalamic nucleus, so that the pallidum also can emit uncontrolled impulses. These impulses are headed for the precentral cortex via the anterior ventral oral thalamic nucleus and nucleus lateropolaris of the thalamus. This may account for the more distal components of the athetotic motor disorder in the extremities. Coagulation of the internal pallidum and the thalamic nuclei receiving impulses from the pallidum can interrupt these two pathways. However, the effect is more efficient and of longer duration if efferent cortical extrapyramidal or pyramidal systems, especially these coming from area 6aα, 6aβ and 4s, are interrupted by additional lesion at the capsular or peduncular level. The resulting hemiparesis can be very slight.

In spite of the fact that the effects of lesions of the subthalamic nucleus in man are in good agreement with those in animals, it is particularly difficult to define the functional role of the nucleus subthalamicus in positive terms. In contrast to numerous observations from human pathology, the experiments of Whittier, Carpenter and Mettler do not indicate that in monkeys there is a somatotopic organization of the nucleus subthalamicus from medial to lateral. On the other hand, there is no doubt about the rather frequent occurrence in man of monoballism of one arm or one leg following a circumscribed lesion in the subthalamic nucleus.

The subthalamic nucleus seems to have overall control of rhythmic movements of the contralateral limbs, especially those for turning around the horizontal, longitudinal and transverse axes. Bucy (21) considers hemiballism as a release phenomenon following suppression of cortical inhibitory mechanisms. Whittier & Mettler (293) consider the subthalamic nucleus as comprised of interneurons of the pallidum system. They believe that its destruction is responsible for an overall disorganization of the pallidum system which leads to excess motor activity.

CENTRUM MEDIANUM. According to current anatomical concepts the centrum medianum receives afferents from the nucleus emboliformis of the cerebellum (83) and the reticular formation, but not, in contrast to previous opinions, from a direct ipsilateral secondary trigeminal pathway. According to the physiological findings of Starzl *et al.* (247), it receives impulses from collaterals of all sensory pathways indirectly through the reticular formation. The centrum medianum is common to all higher mammals. It is independent of the cortex (271) and conveys complex integrated impulses from the cerebellum and reticular formation to both parts of the striatum (83).

Experimental observations in animals will first be considered. Because of the location of Forel's tegmental fascicle or the vestibuloreticulothalamic tract, ipsiversive turning movements were often considered to result from stimulation of the centrum medianum. However, these movements are apparently represented in a pathway which parallels the vestibuloreticulothalamic tract and bypasses the centrum medianum ventrally without entering it [Hassler (89)]. Electrical stimulation of the centrum medianum evokes an arousal reaction and a recruiting response in various cortical areas, especially in the frontal and anterior parietal cortex [Hanbery & Jasper (78)]. Circumscribed lesions in the nucleus ventralis medialis (VM) and ventralis anterior (VA) of the thalamus, if combined with a destruction of the rostral nucleus reticularis thalami, suppress the recruiting response in the frontal cortex. The unspecific projections of the centrum medianum to the parietal cortex are inactivated only by making an additional lesion in the lateral part of the nucleus ventralis lateralis (VL) thalami [Hanbery *et al.* (77)]. This lesion also interrupts the efferent pathway from the centrum medianum to the putamen and caudate nucleus. Thus efferent impulses from the centrum medianum cannot cross to the nuclei of the extrapyramidal system and re-enter the thalamus before going to the cortex. The lesions in VA and VM and in the rostal part of the nucleus reticularis interrupt the last projections to the premotor cortex and probably also the fibers entering the pallidum from below.

The hypnogenic zone of Hess (108) extends to the centrum medianum. Under appropriate environmental conditions low-frequency threshold stimulation of this area can produce a behavioral reaction similar to physiological sleep. This has been confirmed by the electrophysiological experiments of Hess, Akert and Koella (5, 98, 99). The most frequent effects following electrical stimulation are an inhibition of respiratory activity both in frequency and amplitude and a decrease of motor excitability [Hess (108)]. No physiological studies of the effect of acute and chronic destruction of the centrum medianum appear to have been made.

Observations from human pathology will next be presented. In the hereditary form of torsion dystonia the small cells of the centrum medianum projecting to the putamen show primary degeneration [Vogt & Vogt (272)]. This would liberate the putamen from cerebellar and brain-stem reticular control. The nerve cells of the centrum medianum show premature aging and retrograde degeneration following various putamen lesions. The physiological significance of this finding is unknown.

During the successful operations performed by Talairach *et al.* (252) in patients suffering from thalamic pain, the centrum medianum has been coagulated repeatedly in part or has had its efferent fibers interrupted. No expected deficiencies resulted from these lesions. Tonic movements of the mouth were seen as a result of stimulation of the centrum medianum (Monnier and others). In collaboration with Riechert and Mundinger we only rarely observed such effects following stimulation of the centrum medianum during operations for trigeminal neuralgia. Stimulation of the centrum medianum in man produces a recruiting response which appears in all areas of the ipsilateral cortex and also slightly in the contralateral hemisphere. Stimulation at 8 per sec. or more had a definite arousal effect in man (fig. 7). In spite of potentiated anesthesia, patients open their eyes, look around during stimulation and relapse into narcosis as soon as stimulation is discontinued [Hassler (85, 86)]. Partial coagulation of the centrum medianum during operations in the arcuate nucleus for pain relief did not have any apparent effect. However, bilateral lesions of the centrum medianum have not yet been made.

The physiological role of the centrum medianum consists of integrating very heterogeneous sensory and cerebellar impulses and elaborating afferent inflow to the striatal system. It controls the overall excitability of the cortex via the caudate nucleus and putamen and seems to trigger—or to inhibit—the motor components of the mechanisms regulating sleep and wakefulness.

OTHER THALAMIC NUCLEI BELONGING TO THE EXTRAPYRAMIDAL SYSTEM. The overwhelming majority of the efferent pathways leaving the internal pallidum

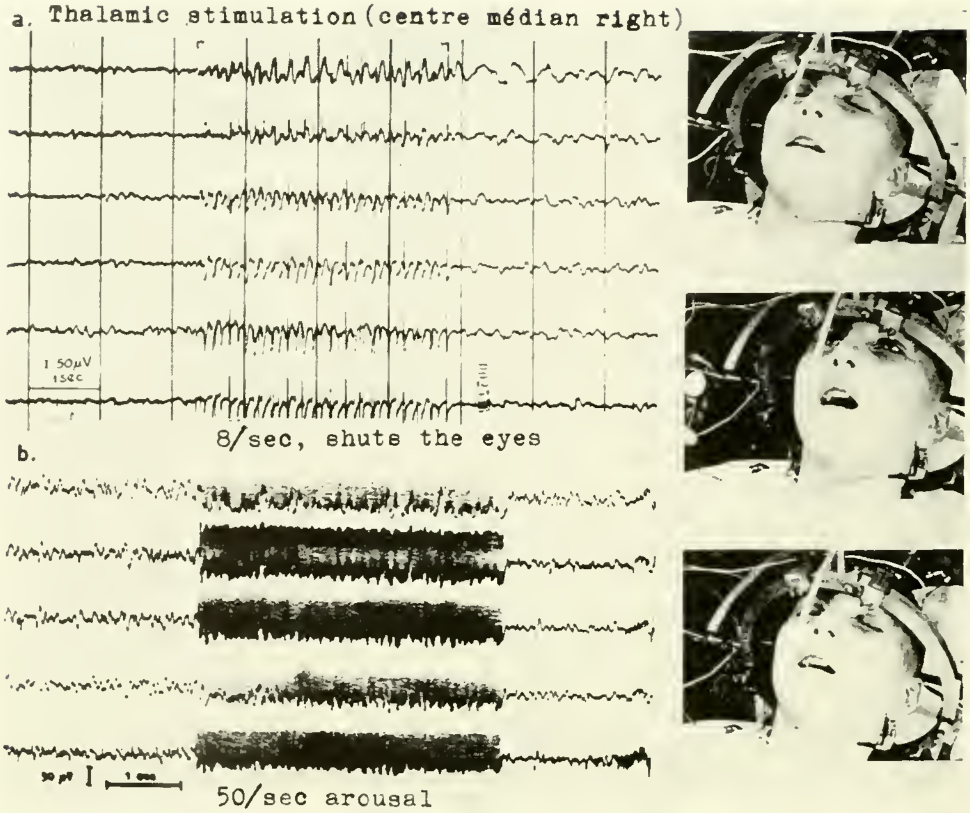

FIG. 7. Effects of stimulation of the thalamus during stereotaxic operations *a*, *b*: 62-year-old man with trigeminal neuralgia. Stimulation of the right centrum medianum 2 to 5 mm above a subsequent thalamotomy in the right nucleus arcuatus. Patient given chlorpromazine. *a:* EEG effects of stimulating with a frequency of 8 per sec. *From top downward:* Right and left precentral region, right and left parietal region, and right and left occipital region. Recruiting waves appear in the right precentral region, slow waves coming on after cessation of stimulation. Patient shuts eyes but remains conscious. *b:* Stimulation at a higher frequency (50 per sec.) induces arousal with opening of the eyes, although EEG waves are not blocked during stimulation. *Upper right:* Control before stimulation of the thalamus. *Middle right:* Behavioral arousal produced by 8 per sec. 9-v. thyratron stimulation of the left anterior lamella medialis thalami in deep chlorpromazine-barbiturate anesthesia. *Lower right:* After thalamic stimulation in a 17-year-old imbecile. [From motion pictures made by Hassler in collaboration with Riechert, Umbach and others; from Jung (135).]

end in the thalamus. These thalamic nuclei receiving afferent inflow from the pallidum may be considered as a part of the extrapyramidal system. The most important are the nucleus ventro-oralis anterior (V.o.a., the ventroanterior part of nucleus ventralis lateralis of Walker, VL) and the nucleus lateropolaris (L.po or VA). The medial nucleus (or nucleus dorsalis medialis thalami) also receives numerous afferents from the pallidum. Nuclei where fiber tracts coming from the nucleus interstitialis, the vestibuloreticulothalamic tract and the brachium conjunctivum terminate are also considered as belonging to the extrapyramidal system, although the brachium conjunctivum should rather be considered as an afferent part of the pyramidal system. As the thalamic nuclei receiving afferents from the pallidum are much smaller in carnivores and rodents than in primates and man, little is known yet about their responses to electrical stimulation in cats.

a) Nucleus ventrointermedius (*V.im*). The nucleus ventrointermedius projects to the cortex. In cats its low-frequency stimulation produces a continuous turning movement of the head or the whole body to the side of stimulation. The same effect is obtained by stimulating its afferent pathway, the vestibuloreticulothalamic tract. Destruction is followed by a

transitory turning movement of the body to the opposite side since this supravestibular system is tonically active during wakefulness [Hassler (89)]. Bipolar stimulation of this nucleus during stereotaxic operations in patients with extrapyramidal motor disorders is followed by a horizontal conjugate ocular deviation to the side of stimulation. In man coagulation of parts of the nucleus produces a paresis of ocular movements with nystagmus to the damaged side which, however, disappears after 1 or 2 weeks. These observations seem to indicate that the nucleus ventrointermedius plays the same functional role in man as in cats where it represents a part of the mechanism responsible for ipsiversive turning movements.

b) Nucleus ventrocaudalis thalami (VPL and VPM). A remark appears appropriate at this point concerning the motor effects following stimulation of the medial lemniscus and the spinothalamic tract or of their terminal thalamic nuclei, the nuclei ventrocaudalis externus (V.c.e.), internus (V.c.i.) and parvocellularis (V.c.pc) (VPL, VPM and VPI, according to Walker's terminology). In unanesthetized, freely moving cats low-frequency stimulation produces twitching of the contralateral face and of the contralateral foreleg—rarely of the hind leg—which is at first synchronous with the stimulus but very shortly shows definite summative effects (such as closing of the eyelids or lifting of the bent foreleg). After the end of the stimulation some, but not all, of the cats may shake the extremity involved or may lick themselves as if an unpleasant sensation had been experienced in the twitching area.

During stereotaxic operations for the relief of chronic intractable pain, the sensory relay nuclei of the thalamus were stimulated in conscious patients. Synchronous muscular twitching accompanied by a twitching or electrifying sensation in the topically corresponding area of the body was evoked with a stimulus frequency up to 8 per sec. When stimulation of the parvocellular and ventral parts of the nucleus (V.c.pc or VPI) at a rate over 20 per sec. produces localized pain (in amputees it may even evoke phantom pains), the ipsilateral motor symptoms are enhanced and extreme pain distortions appear. When stimulation does not produce painful sensations, these distortions apparently have to be considered as reflex motor activities resulting from extero- or proprioceptive impulses aroused artificially by electrical stimulation of central sensory systems. These effects are not extrapyramidal motor phenomena in the narrow sense.

c) Nucleus ventro-oralis posterior. Stimulation of this nucleus and of the terminal dentatothalamic fibers of the brachium conjunctivum with the Hess method causes movements of the contralateral forelegs and of the contralateral muscles of the face. The foreleg is lifted or adduced and stretched forward. This adducting and forward stretching effect is also seen after stimulation of the brachium conjunctivum in the area between its decussation in the mesencephalon and the cerebellum where the effect is only homolateral. These motor effects obviously are due to stimulation of afferent fibers going to area 4. According to Hess, coagulation of small parts of this nucleus has no effect. Larger lesions (2 to 3 mm in diameter) cause functional disabilities such as diminished use of the limb, lack of postural control and ataxia.

In man this nucleus (V.o.p.) has been stimulated by Hassler, Riechert and Mundinger during stereotaxic operations, however, only in patients suffering from myoclonic or parkinsonian disorders. When the myoclonic movements or the resting tremor disappear during light anesthesia, bipolar low-frequency stimulation can cause them to reappear in the contralateral limbs after a short latency. The frequency of the hyperkinesia differs in this case in the arms and in the legs. If the resting tremor persists during the operation, it is possible to change its frequency by using the same type of stimulation and to block it in regular intervals. Single shocks cause an enhanced flexion or extension of the forearm with compensatory intervals, depending upon the phase of the concomitant tremor. Therapeutic destruction of this nucleus to a considerable extent reduces or completely suppresses both resting tremor and myoclonic movements. Larger lesions can produce a contralateral ataxia which is later compensated. Diminished use of the extremities is also seen, but no pareses and no increase of tone. Lesions extending to more medial areas produce a paresis of mimetic movements of the contralateral facial muscles with completely intact voluntary motor activity. Disorders of sensibility never occur following lesions in the ventro-oral thalamic nuclei. The effects of clinically occurring focalized lesions in this nucleus in patients without previous extrapyramidal motor disorders include a diminished use of the extremities without paralysis, contralateral ataxia, and contralateral mimetic paralysis of the facial muscle as von Leyden and Nothnagel had already assumed. Interruption of the dentatothalamic fibers of the brachium conjunctivum terminating in this nucleus produce the same effect. This is in contrast to the results of the monkey experiments of Carrea & Mettler (35) and Carpenter (30).

d) Nucleus ventro-oralis anterior and nucleus lateropolaris. The effects of stimulation or destruction of these nuclei which receive afferents from the pallidum are not well known in cats because of their small size. Both nuclei are much larger in man than the thalamic terminal area of the brachium conjunctivum. Stimulation of these nuclei in Parkinson's disease, especially of V.o.a., produces an acceleration and an increase of the resting tremor or transitory block due to interference of the spontaneous rhythm with the stimulus frequency. The effects of stimulation are less clear than those following stimulation of the nucleus ventro-oralis posterior. In athetosis, torsion dystonia, ballism and chorea, it is possible to trigger the hyperkinetic phenomena during quiet intervals by stimulating nucleus V.o.a. and L.po. The hyperkinesia produced by electrical stimulation outlasts the end of the stimulation. In some conscious patients with a parkinsonian syndrome, stimulation of this nucleus was followed by conjugate eye movements to the contralateral side (the head being fixed), concomitant violent lifting of the contralateral arm and excited utterance of unintelligible sounds comparable to the syndrome described as following stimulation of Penfield's supplementary motor area.

Destruction of both nuclei in patients with torsion dystonia and athetosis improves and sometimes even suppresses the hyperkinesia without causing any paralysis. In athetosis, however, the symptoms usually reappear. Simultaneous destruction in Parkinson's disease of nucleus V.o.a. and V.o.p. decreases or even completely abolishes the rigor. At first there is even a hypotonia, although the paralysis is very slight or even absent. Previously missing associated movements may reappear. The posture is so fundamentally changed after such operations that it is almost impossible to recognize the previous parkinsonian disease in these patients. Postoperative motor impairment has not been observed. Some of the patients, however, have to be persuaded after the operation to persevere in using the limb previously immobilized by rigidity. Learned movements are also unimpaired. Bilateral symmetrical lesions are contraindicated because of the consequent personality changes of the frontal lobe type which result from the interruption of passage fibers of thalamofrontocortical pathways.

e) Nucleus ventro-oralis internus. Stimulation of this nucleus and of its afferent fiber tracts from the nucleus interstitialis produces a rotary movement of the head to the ipsilateral side. In cats the effect involves the head and the anterior body. Destruction produces only very transitory effects such as a rotation of the head to the opposite side. The sites of stimulation for the arrest reaction described by Hunter & Jasper (122, 123) are located in the medial part of this nucleus (close to the anterior intralaminary nuclei). In man stimulation of this nucleus produces a contraction of the muscles of the contralateral neck and shoulder, of the sternocleidomastoid and of the facial muscles. Simultaneously, an arousal effect sometimes with smiling appears. In spasmodic torticollis, destruction of this nucleus reduces the rotary movements to the ipsilateral side but not to such an extent that it would be sufficient by itself for a satisfactory therapeutic effect.

Mesencephalic Structures

NUCLEUS NIGER. Early studies of the effects of stimulation of the region of the nucleus niger in animals, made by von Bechterew (273), Jurman (139) and von Economo (274), showed bilateral rhythmical chewing and swallowing movements to be the principal motor responses. However, later investigators failed to find any definite motor effects.

According to Mettler (181) stimulation of the nucleus niger increases the extensor tonus of both anterior limbs in cats, even after destruction of the motor cortex. Mettler and co-workers (184) also thought that stimulation of the nucleus niger reduces the amplitude of the phasic movements resulting from simultaneous cortical stimulation and tends to produce a tremor. As Folkerts & Spiegel (60) were able to show, stimulation of the reticular formation produces tremor only when the nucleus niger had been previously destroyed. Wycis *et al.* (297) showed that this tremor could be obtained also after degeneration of the brachium conjunctivum, thus demonstrating that it does not depend on participation of the brachium conjunctivum. This is in contrast to the view of Carrea & Mettler (35) who considered lesions of the ventral part of the brachium conjunctivum to be responsible for the tremor without stimulation.

According to older observations destruction of the nucleus niger in dogs and cats does not usually produce disorders of motor activity or muscle tone [von Bechterew (273), von Economo & Karplus (275)]. Only D'Abundo (37) observed choreoid movements and later rigor in newborn cats following lesions in the substantia nigra and in parts of the mesencephalon. Bishop *et al.* (12) and also Peterson *et al.* (210) were able to produce postural tremor by means of small localized lesions in an area dorsal and medial to the nucleus niger, intermediate between

it and the nucleus ruber. They probably interrupt at least partially the ascending efferent fibers from the nucleus niger. According to Whittier & Mettler (293), their lesions responsible for a static tremor are located more rostrally and dorsally to the substantia nigra.

Observations from human pathology are particularly important here since experiments in animals do not give definite information concerning the functional significance of the nucleus niger. On the basis of three cases with localized lesions, Brissaud (14) was the first to assert that destruction of the nucleus niger is responsible for parkinsonism. The later observations of Trétiakoff (258), Foix (59) and Spatz (237) pointed to the nucleus niger as being the site of major damage in postencephalitic parkinsonism. Genuine paralysis agitans is also due to cell destruction specifically localized in the nucleus niger [Hassler (79)]. The tremor (without rigor and akinesia), in the contrary, is caused by a diffuse lesion (*état préciblé*) of the striatum [Hassler (80)]. Rigor and akinesia, the two other motor components of parkinsonism, are caused by lesions in the nucleus niger, mainly in its posterior portion. In most patients with this disorder significant pallidum lesions are missing [Hassler (79), Klaue (149)].

The mechanisms of resting tremor, akinesia and rigidity are now better understood as a result of the stereotaxic operations which have recently been performed on patients suffering from parkinsonian disorders. In 1817 James Parkinson had already described the disappearance of resting tremor following a subsequent hemiplegia. Bucy (20, 22, 25) could very definitely reduce or even abolish the resting tremor by resection of the arm area in the precentral gyrus and of area 4 gamma. The same effect was obtained by Putnam (215) following unilateral pyramidotomy in the spinal cord. In both cases the effect was associated with a contralateral hemiparesis. The tremor reappeared as soon as the paresis disappeared. Hence it must be concluded that the tremor depends upon a facilitatory influence of the pyramidal tract on the anterior horn mechanisms. A continuous flow of subliminal pyramidal impulses influencing anterior horn cells has been demonstrated electrophysiologically by Adrian & Moruzzi (1). The tremor frequency, however, is not the same as the spontaneous rhythmic activity of the cortical motor areas [Schwab & Cobb (230), Jung (130)]. Its rhythm probably is not produced by cerebral mechanisms but by bulbospinal interneurons; it is thus understandable that the ipsilateral tremor is rarely synchronous in arm and leg [Jung (130)].

In an effort to suppress the pyramidal facilitation of the tremor without producing a hemiparesis, Hassler and associates destroyed stereotaxically the nucleus ventro-oralis posterior of patients with Parkinson's disease. This was intended to abolish the afferent inflow from this nucleus to area 4γ of the cortex, while leaving the efferent pyramidal path intact. The result was a definite decrease or even suppression of the contralateral resting tremor. If the tremor temporarily disappears before coagulation, it can be evoked by low-frequency stimulation of the nucleus V.o.p.; if the tremor persists, it may be enhanced, accelerated or blocked by such stimulation. Single shocks enhance the momentary phase of the tremor which is followed by a compensatory interval in either flexion or extension; stimuli at 4 per sec. slow the tremor, at 8 per sec. they accelerate it, while at higher frequencies it is blocked. Similar but less definite effects may be obtained by stimulating the nucleus ventro-oralis anterior (V.o.a.), which is a terminal nucleus for fibers coming from the internal pallidum (H_1 of Forel). Thus, bipolar stimulation of the internal pallidum also causes similar but less marked changes in the tremor. The internal pallidum projects via V.o.a. to the area $6a\alpha$ in the precentral gyrus where many fibers of the pyramidal tract originate. Thus, this part of the afferent pyramidal pathway is also capable of influencing the tremor frequency, although the effect is less marked than that of V.o.p.

A complete and permanent suppression of the resting tremor seems to result only from either a lesion of the pyramidal tract causing a hemiparesis or a lesion of the thalamofrontocortical pathways producing personality changes with decreased emotional responsiveness. The emotional enhancement of the resting tremor can be suppressed by prefrontal lobotomy. One may conclude therefore that in parkinsonian disease prefrontal cortical areas exert their descending corticifugal influence during emotional stress by means of prefrontoreticular and prefrontopallidal pathways, and in cases of genuine tremor with an intact nucleus niger also via prefrontonigral fibers. Definite improvement, however, can be produced by coagulation of the oral ventral nuclei of the thalamus (V.o.a. and V.o.p) or of the pallidum without undesirable side effects (86, 88, 90).

These therapeutic effects provide evidence of facilitatory influences both from afferent and efferent pyramidal pathways and prefrontal systems upon the

interneuronal mechanisms of the anterior horns producing tremor. Does the resting tremor depend upon peripheral reflex mechanisms, especially afferent impulses from muscle and tendon spindles? Foerster (57) and Pollock & Davis (211) observed that severing of the dorsal roots does not reduce the resting tremor but makes it coarser and more irregular. Suppression of the muscular afferents by means of novocaine injection into the muscle also does not decrease but rather enhances the tremor, whereas the rigor disappears while muscular strength is unimpaired [Walshe (289)]. Thus it seems that resting tremor is mostly not dependent upon the stretch reflexes of the muscles or their so-called 'external loops.' The circuit controlling muscle length (with its receptor in the annulospiral endings) sends inhibitory and regulating impulses through muscle afferents to the interneuronal anterior horn mechanisms which generate the tremor rhythm.

Furthermore, the interneurons of the anterior horn generating the tremor are controlled by synchronizing and desynchronizing reticulospinal influences [Magoun & Rhines (174, 175), Niemer & Magoun (201)]. The desynchronizing influence which at the same time inhibits the slow myotatic reflexes of the parkinsonian syndrome seems to originate in the strionigral system and to use nigroreticulospinal pathways as efferents. Following deficiency of this desynchronizing effect in the parkinsonian syndrome, descending pallidoreticular influences originating in the external pallidum and exerting a synchronizing effect predominate and enhance myotatic reflexes. Simultaneously enhanced by facilitatory pyramidal impulses, these influences induce the interneuronal system of the spinal cord to produce the rhythmical tremor activity. Thus, destruction of the niger cells upsets the balance between one synchronizing and one desynchronizing system and, accordingly, the tonic and synchronizing influence of the pallidum predominates. Enhancement of the tremor following stimulation of the pallidum and its permanent improvement following coagulation of the pallidum confirms this concept of the origin of the resting tremor of parkinsonism. (See also the discussion of tremor in the later section of this chapter concerned with extrapyramidal influences on reflex activity.)

A definite sign of a nucleus niger lesion in man is the increase of muscle tone, the rigidity which is characteristic of parkinsonism. The results of surgical therapy of the rigidity are clearer than those for resting tremor. Muscular resistance to passive movements in this state is different from that in spasticity. It is not elastic but viscous, adapts by lengthening or shortening to any new, passively imposed muscle length and maintains constant the strength of its resistance to passive movement. According to von Holst (280) the automatic muscle tension regulator is in action alone in rigidity, adapting the muscle length to every new limb position but maintaining the muscle tension constant. The inhibitory Golgi tendon organs and the facilitatory flower-spray endings on the intrafusal muscle fibers of the muscle spindles [Hassler (88)] are receptors for muscle tension. In parkinsonian rigidity a suppression of the circuit controlling muscle length is suggested by the maintenance of muscle tension and by the absence of increased and irradiating tendon reflexes.

According to Sommer (236) and Hoffmann (118) a gamma innervation of the muscle spindles is responsible for the Jendrassik's sign and other reflex enhancing mechanisms. Since in most parkinsonian patients such reflex enhancing mechanisms do not affect the rigid muscles (see fig. 21), there is probably in them a deficient activity of central supranuclear mechanisms for gamma innervation. However, in parkinsonism the central excitability of the gamma fibers is suppressed only for phasic proprioceptive reflexes and not for myotatic reflexes [Schaltenbrand & Hufschmidt (224)]. The responsiveness of gamma cells to exteroceptive stimuli also remains unimpaired. A central stimulation of the gamma cells still seems to be possible during rigidity involving pathways other than those active during reflex-enhancing procedures. Granit & Holmgren (70) discovered two different central pathways conveying impulses from the mesencephalon to the gamma cells, a fast-conducting pathway in the lateral funiculus crossing to the opposite side, and a slow pathway with so many synapses that an almost total section of the spinal cord is necessary to interrupt it completely. Only the fast-conducting central pathway for gamma innervation, which appears to be identical with the nigroreticulospinal system, is deficient during rigidity.

During many movements gamma innervation precedes the alpha innervation, the former having a kind of 'starter function'; it is precisely this function, however, which is missing in parkinsonism, in which the greatest difficulty is in the starting of a movement. This accounts for the loss of a considerable number of involuntary movements, such as the spontaneous synergic and associated movements. The impairment of voluntary motor activity in general may

also be explained by this deficiency of the central mechanism triggering the so-called 'external loop.' This rapid gamma innervation of the muscle spindles belongs essentially to the control circuit regulating the length of the muscle in so far as it provides the possibility of adjusting the sensitivity of the annulospiral receptors. If this rapid central gamma innervation is missing, a phasic proprioceptive reflex may still result from a sudden change in the length of the muscle, whereas the continuous control and maintenance of the muscle length and its adaptation to modified initial length becomes impossible. Hence, muscle length is not kept constant in muscular rigidity—in contrast to spasticity—but changes in accordance with external forces. On the contrary, in parkinsonism muscle tension is maintained constant against all external influences by the intact regulators of muscle tension.

In spite of the loss of central gamma innervation, the peripheral gamma neurons remain morphologically intact for a long time. As the investigation of Byrnes (29) showed, morphological changes are seen in muscle spindles and their innervation only in cases of rigidity of more than 10 years duration. To a large extent the increase in muscle tone in rigor is due to an enhancement of the myotatic reflexes, that is of the tonic component of the stretch reflexes, whereas there is no enhancement of the phasic (monosynaptic) stretch reflexes.

The reflex character of the so-called plastic muscle tone, which is a component of rigidity, has been demonstrated by its suppression following dorsal root section [Foerster (57), Pollock & Davis (211)] or elimination of muscle receptors by means of novocaine injections in the muscles [Walshe (289)]. Simultaneously, there is no impairment of muscular strength. After suppression of all muscular afferents, the previously rigid limb no longer adapts to changes in length by maintaining a constant muscular tension and also is unable to regain it. This plastic muscle tone is only one component of rigidity. In Pollock & Davis' case of parkinsonism, contractures developed in the biceps, the flexor carpi ulnaris and the palmaris longus 11 days after complete deafferentation of the arm by means of rhizotomy which included C 4 to T 4. This so-called resting rigidity following complete suppression of the component sustained by reflex mechanisms is caused by descending central influences originating in the brain stem and impinging upon the alpha cells; this type of rigidity is independent of the 'external loop.' It also could not be diminished by novocaine injections in the muscle; it did, however, disappear during sleep. When the head of the patient, spontaneously turned toward the side opposite to the deafferentation, was turned back to the side of the deafferentiated arm, the tonic contraction was diminished in the flexor muscles of this arm [Pollock & Davis (211)].

Both plastic muscle tone and resting rigidity are slightly decreased following interruption of the pyramidal tract, as by Putnam's pyramidotomy. Destruction of the caudate nucleus has no effect on the contralateral muscular resistance [Meyers (186, 187), Browder (17)]. However, contralateral rigidity decreases if the anterior limb of the internal capsule and anterior parts of its posterior limb are simultaneously severed [Meyers (187, 188)]. Destruction of the ansa lenticularis, either by direct exposure or by stereotaxic methods, caused an improvement in rigidity which was more pronounced than following other types of operations (Meyers, Fénélon, Spiegel and Wycis). Destruction of the pallidum either by electrolytic lesions [Spiegel & Wycis (240–242)], by procaine-oil injections [Narabayashi & Okuma (199, 200)] or thermocoagulation (Leksell, Talairach, Guiot, Hassler and Riechert) removes contralateral rigidity. The same effect can be obtained by coagulating the nucleus ventro-oralis anterior (V.o.a.) of the thalamus [Hassler & Riechert (86, 92)] where the fibers form the internal pallidum terminate. Thus, a lesion of the pallidum, or destruction of the pallidocortical systems suppresses the rigor produced by nucleus niger lesions. This is not consistent with the earlier but now unacceptable pallidal theory of parkinsonism which assumed that lesions in the pallidum are responsible for rigidity and akinesia.

The interruption of the pallidal system, where it may occur, obviously produces—at least in part via efferent corticospinal fibers from area 6aα—a loss of the synchronizing and facilitatory influences upon the interneuronal-anterior horn mechanisms. This not only suppresses the enhancement of the myotatic reflexes but also the descending impulses generating resting rigidity. If the predominance of the peripheral mechanisms controlling muscle tone is thereby suppressed, plastic rigidity with stretch and shortening reactions also disappears. If the ansa lenticularis and the external pallidum are simultaneously destroyed, the therapeutic effect may in part be due to the suppression of the direct descending pallido-reticulospinal influences upon the anterior horn system. However, this explains parts of the effects only. It does not explain the effect of localized lesions restricted to the internal pallidum and in particular

not that of lesions in adjacent neuronal relays (such as V.o.a. or H_1). The efferent pathway from the internal pallidum terminates in the nucleus ventralis oralis anterior of the thalamus (V.o.a.). This nucleus has no descending connections but projects to the precentral cortex in the neighborhood of area 6aα. Accordingly, pallidal impulses also have a facilitatory influence on the interneuronal mechanism of the spinal cord via pallidothalamoprecentral fibers and the corticospinal or pyramidal tract. Suppression of this pyramidal facilitation also produces a decrease in the myotatic reflexes and a decrease in the impulses for resting rigor. There is no full explanation, however, for the fact that interruption of the pyramidal tract is much less effective in reducing rigidity than is the interruption of a certain number of its afferents. This may be related to inhibitory and excitatory impulses in the pyramidal tract itself, which are evoked by other afferents.

Suppression of rigor in parkinsonism also improves posture and the control of motor activity which may even become normal. It was surprising that even the hypokinesia or akinesia, the so-called *rigorfreie Starre* of Bostroem, normally considered as an independent sign of parkinsonism, was improved or suppressed after the operation and that even previously lost associated movements reappeared. Hence, it may be concluded that their mechanism seems to be closely related to that of rigor.

In trying to define the functional role of the nucleus niger one must emphasize rigidity and akinesia as the most important symptoms of its destruction. A positive function of the nucleus niger in the author's opinion might be supranuclear control of the gamma neurons of the anterior horn and an inhibition of myotatic reflexes. As described above, the gamma innervation often starts earlier than the alpha innervation; thus the 'starter function' of the nucleus niger in voluntary motor activity facilitates phasic muscle innervation, the rapid onset of a movement, associated movements and many automatic movements. The role of this 'starter function' in 'ereismatic' or supportative aspects of voluntary movement will be considered later in this chapter.

In this connection we must emphasize the striking melanin pigmentation of the niger neurons. It is most conspicuous in man but is also found in monkeys and in old horses. Melanin is an end product of metabolic processes involving dihydroxyphenyl derivates, such as epinephrine and norepinephrine. Since melanin depots are found in the adrenal medulla, it may be suggested that the nucleus niger also may produce epinephrine as a transmitter substance. As Marrazzi & Marrazzi (177) showed, epinephrine may have an inhibitory effect on the anterior horn cells. Therefore, one might expect that the nucleus niger exerts its inhibitory influence on tonic muscular innervation and myotatic reflexes in part by means of an adrenergic transmitter mechanism. But the facilitation of tremor by epinephrine and the beneficial effect in man of parasympathicolytic agents on symptoms of nucleus niger lesions makes this speculation unlikely.

NUCLEUS RUBER. The effects of stimulation and destruction of the nucleus ruber are very contradictory. For this there are three main reasons. *a)* Anatomically the nucleus ruber is not a homogeneous structure; its various components are hardly comparable in different animal species. *b)* It is crossed by the brachium conjunctivum; however, only a few fibers of this important tract terminate in the nucleus ruber. *c)* It is surrounded by a great number of structures with motor functions unrelated to the nucleus ruber. In order to decrease these difficulties, we shall distinguish between experiments in rodents and carnivores, on the one hand, and findings in primates, including man, on the other. In rodents and carnivores the major part of the nucleus ruber is constituted of large cells; its efferent pathway is the crossed rubrospinal tract. In primates and in man, on the contrary, small cells predominate in the nucleus ruber and its efferent pathway passes through the central tegmental tract to the lower olives and the reticular formation. An accurate interpretation of the work of Mettler and his co-workers, especially of Carpenter's findings (30), is not possible as long as the fundamental fact is not taken into account that, in primates, the nucleus ruber neurons pass through the central tegmental tract. Walberg's (284) findings also are not in conflict with this fact.

Both in dogs and cats and in monkeys and chimpanzees stereotaxic stimulation of the nucleus ruber area in the mesencephalon produces a pattern of motor activity characterized by a concave bending of the trunk and the neck toward the stimulated side, a phenomenon known as the tegmental reaction. This is a partial manifestation of the turning movement to the ipsilateral side performed by the animal when it is tied up or when its movements are restrained, as shown by Ingram, Ranson and Hannett in cats. Such results also have been obtained by Kure *et al.* (154) in dogs, by Mussen (198) in cats, and by Mettler *et al.* (184) in cats and monkeys. However,

as the investigations of Ingram *et al.* (128) showed, this effect is not due to the excitation of rubral elements but is produced by stimulation of the reticular formation and of its fiber tracts in the whole area extending from the caudal subthalamus to the caudal pons.

The existence of a pathway extending from the pons to the thalamus and responsible for the so-called tegmental reaction is confirmed by Hess' extensive stimulation and destruction experiments. In unanesthetized unrestrained cats it can be shown to mediate ipsiversive bending. The responsible fiber tract is the tractus vestibuloreticulothalamicus (89).

Rotation of head and anterior body, occasionally also considered as effects of ruber stimulation, are not caused by stimulation of the ruber itself but of the dorsomedially located and very excitable tractus interstitiospinalis [Hassler & Hess (91)]. As Hess also showed, very small stimulating electrodes in the nucleus ruber may also produce contralateral movements of the limbs and the facial muscles. These movements are caused by stimulation of the fibers of the brachium conjunctivum crossing the nucleus ruber.

The purest effect of ruber stimulation is obtained in rodents where it is possible to perform an almost isolated stimulation of its efferent pathway, the rubrospinal tract. In cats rubrospinal stimulation causes raising of the head and the anterior body, as Hess & Weisschedel (112) first demonstrated and as one of us [Hassler (89)] could confirm by study of the Hess material. This movement is not necessarily the only effect produced by stimulation of the large cell elements of the nucleus ruber; however, it is the only clearly demonstrated effect. The distribution of the ruber neurons within the nucleus is so sparse that a stimulus intensity producing definite effects by stimulation of fiber tracts in the neighborhood is still too weak to stimulate enough ruber cells to yield a visible motor effect.

Destruction of the nucleus ruber in cats [von Economo & Karplus (275), Rademaker (216), Mussen (197), Ingram & Ranson (126)], which contains large cells, produces only a short transitory unsteadiness in gait and ataxia with overstepping if the destruction is extensive enough to cause a definite degeneration of the rubrospinal tract. A contralateral decrease of muscle tone and proprioceptive reflex activity should also be seen after this type of lesion as well as turning postures or turning movements. The latter are due to a concomitant lesion of the mesencephalic reticular formation and of the ipsilateral vestibuloreticulothalamic pathway. As Ingram *et al.* (127) demonstrated, localized ruber lesions do not produce impairment of labyrinthine and body righting reflexes, as Rademaker thought, but only impairment of placing and hopping responses in dogs.

In cats changes of muscle tone following bilateral lesions in the nucleus ruber are reported to be variable; an extensor rigidity and increased resistance to passive movement has frequently been described [von Economo & Karplus (275), Rademaker (216)]. The latter considered this extensor rigidity primarily as a result of the interruption of Forel's tegmental crossing of the rubrospinal tract. However, as Hess has shown, circumscribed destruction of the rubrospinal decussation and of the higher parasagittal mesencephalic areas produces in cats a loss of the lifting movements with a permanent lowering of the head. The extensor rigidity earlier described is probably due to the fact that certain other mesencephalic structures are simultaneously seriously damaged. von Economo & Karplus, as well as Lafora, had previously observed slow involuntary movements comparable to athetotic-choreiform hyperkinesia following unilateral or bilateral lesions of the nucleus ruber. Recently Lafora (156) again emphasized the presence of such hyperkinetic symptoms following ruber lesions.

In monkeys destruction of the nucleus ruber or interruption of one rubrospinal tract causes asynergia and a coarse tremor with unimpaired postural reflexes [Keller & Hare (142)]. This effect seems to be due to the interruption within the red nucleus of fibers coming from the brachium conjunctivum. According to Mettler and Carpenter, interruption in the macaque of the brachium conjunctivum fibers leaving the red nucleus in a rostral direction toward the thalamus does not have any significant effect. Therefore, the very thin rubrospinal tract is considered in monkeys as responsible for the tremor, ataxia and asynergia following lesions of the brachium conjunctivum. In the macaque unilateral or bilateral lesions of the red nucleus produce, according to Mettler, a transitory ataxia, asynergia and tremor from which the animals completely recover. Only after very extensive bilateral lesions of the nucleus ruber does the animal show a specific additional impairment, a hypokinesia, which, however, does not impair motor dexterity. In monkeys Carpenter did not observe any hyperkinesia following localized destruction of the nucleus ruber.

In clinical neurology an upper and a lower ruber syndrome are recognized. The upper syndrome [Chiray *et al.* (36)] consists of hemiataxia and hemi-

paresis (often hypotonic) with a coarse static and action tremor on the contralateral side combined with disorders of articulation. Benedikt's lower ruber syndrome is characterized by an ipsilateral paralysis of the oculomotor nerve combined with a contralateral hemiasynergia, unilateral athetotic movements with rhythmical myoclonic activity of the extremities, or a coarse contralateral tremor. The occasional muscular rigidity is probably due to a simultaneous lesion of the adjacent nucleus niger. Particularly uncomplicated cases of ruber lesions were described by von Halban & Infeld (277) and Marie & Guillain (176). In the cases with a long history the clinical picture showed a spastic hemiplegia with contractures and athetotic movements.

In summary, it may be said that the most evident symptoms following destruction of the nucleus ruber in monkeys and man are static tremor, choreoathetosis and sometimes myoclonic disorders of the contralateral side. In carnivores these disorders are not regularly produced; instead the most consistent effect of stimulation is a lifting of the head and anterior body. A better understanding of nucleus ruber function could be obtained by stimulating and coagulating the nucleus ruber following previous degeneration of the brachium conjunctivum fibers. This type of experiment has been done by Wycis *et al.* (297) who found that the resting tremor is not consistently changed after destruction and degeneration of the brachium conjunctivum. According to our view of its place in the motor fiber systems, the small cells of the nucleus ruber play an essential role in the control of the motor systems of the cerebral cortex. As was pointed out in the chapter dealing with the efferent mechanisms, the nucleus ruber sends cerebellar impulses via the central tegmental tract and inferior olives back to the cerebellar cortex.

Statokinetic and Locomotor Structures in Brain Stem

The central statokinetic mechanisms control the posture and motor activity of the body itself, in contrast to the teleokinetic mechanisms necessary for reaching objects outside of the body. The statokinetic systems also are responsible for establishing and maintaining the equilibrium of active posture during wakefulness. As the basic 'start position' the latter is a prerequisite for spatial orientation by means of the various sensory systems and for consequent purposive actions.

The semicircular canals, the otoliths and the neck receptors are the sensory systems essential for statokinesis. The otoliths are responsible for the continuous presence of tonic vestibular reflexes which do not show adaptation to the stimulus. Cephalad to the level of Sherrington's intercollicular decerebration we find the mechanisms mediating the functions that Magnus, De Kleijn and Rademaker called *stellreflexe* which control body posture, standing and locomotion and provide stability even against suddenly disturbing factors. Using these proprioceptive locomotor mechanisms, animals lacking higher brain structures can move around freely and counteract external influences on their movements as long as olfactory or visual perception is not necessary. The semicircular canals provide the statokinetic systems with impulses making possible compensation for passive angular acceleration. The otoliths are used to compensate for rectilinear acceleration and to correct modified posture, whereas proprioceptive impulses from the muscles, especially from those of the neck, correct changes in posture of the various parts of the limbs and the relation of the parts of the body to each other.

At their highest level the statokinetic systems are divided into several neuronal mechanisms, each of which regulates movements in one direction in space. However, these directions in space are not identical with the positions occupied by each pair of semicircular canals. The latter therefore do not correspond directly to these central representations of forces for movements in the various directions of space: turning to the ipsilateral (ipsiversive) or contralateral (contraversive) side in the horizontal plane, upward and downward movements in the vertical plane, as well as rotation around the longitudinal axis of the body in the frontal plane.

A survey of the neuronal mechanisms for the direction-specific movements which can be evoked by mesodiencephalic stimulation appears in figure 8. A topographical representation of the diencephalic areas yielding such responses will be found in figure 9.

NEURONAL MECHANISMS OF ROTARY MOVEMENTS AROUND LONGITUDINAL AXIS. Using weak monopolar stimuli and thin electrodes, Hess (100, 101, 107) was able to produce rotatory movements of the head around the longitudinal axis toward the side of stimulation in unanesthetized unrestrained cats. If low-frequency stimulation is used, each stimulus induces a rotatory movement, the head partially returning to the original position in the interval separating two stimuli. Sometimes the rotation also involves the anterior part of

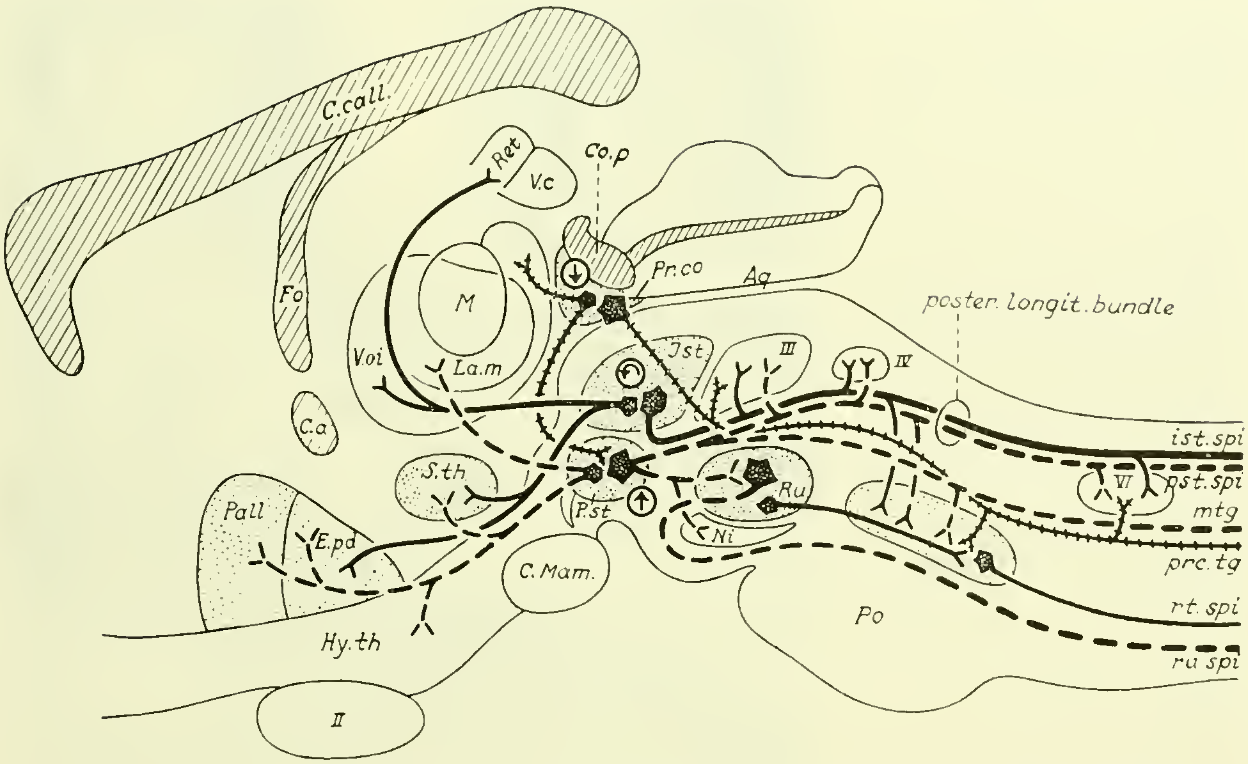

FIG. 8. Diagram of nuclei and tracts involved in posture and responsible for direction-specific motor effects of mesodiencephalic stimulation. Rotation movements are regulated by the interstitial nucleus (*Ist*) and its fiber systems (——). Raising movements are regulated by the praestitial nucleus (*P.st*) and its fiber systems (-----). This tonically active nucleus sends short fibers to the nucleus ruber magnocellularis (*Ru*) from which arises the rubrospinal tract (*ru. spi.*). Lowering movements are regulated by the praecommissural nucleus (*Pr. co*) and its fiber systems (+++++). The efferent fibers constitute the praecommissurotegmental tract. All descending fiber tracts of the direction-specific systems send collaterals to the nuclei of the ocular muscles (*n. III, IV* and *VI*) and the reticular formation.

the body or even the whole body in such a way that the cat rolls around its longitudinal axis. In unrestrained animals the position of the eyes is normal in relation to the head. However, if the head rotation is impossible, an intermittent rotation of both eyes in the same direction appears which is easy to recognize because of the slit-shaped pupils. In *encéphale isolé* cats, where head rotations are impossible, stimulation of the same central area produces only conjugate rotatory eye movements [Hyde & Eliasson (124, 125)].

Coagulation of an area producing rotatory movements is followed by a mirror-image defect: the head of the cat is continuously rotated to the opposite side, while the eyes are kept in normal position in relation to the head (fig. 10). Electrical stimulation of the coagulated area has no effect. These mirror-image disorders usually last over a period of several days and then disappear slowly. However, they also can last several months.

The mirror-image defect is attributable to the fact that under normal conditions the mechanisms for rotatory movements in both hemispheres are in tonic activity during wakefulness and that there is a balanced relationship between both sides which assures the head of being kept in the normal position. Following destruction of one mechanism, the other side becomes predominant and produces rotation of the head toward its side.

The mechanism responsible for rotation around the longitudinal axis lies in the nucleus interstitialis of Cajal with its descending and ascending connections [Hassler & Hess (91)]. Its large nerve cells give rise to the particularly large interstitiospinal

fibers, which constitute the medial border of the fasciculus longitudinalis medialis. They send collaterals to all the eye muscle nuclei (fig. 8) and terminate in the interneurons of the anterior horn of the cervical cord and in the nucleus of the accessory nerve. In all experiments yielding a permanent rotatory posture of the head these fibers show degeneration (see fig. 10). These findings confirmed the conclusions of Muskens (196) whose lesion experiments in 1914 had led him to regard this structure as responsible for rotatory postures.

Furthermore, many fibers also leave the nucleus interstitialis in rostral and lateral directions. It is not yet known whether these fibers are collaterals of the interstitiospinal fibers or whether they are axons of smaller nerve cells of the nucleus interstitialis. In the rostral direction fibers go (fig. 8) *a*) to the nucleus ventro-oralis thalami (V.o.i.), *b*) to the nucleus reticulatus thalami, laterally from the ventrocaudal nuclei, and *c*) to the nucleus entopenduncularis and nucleus subthalamicus via the ansa mesencephalica ascendens. Weak stimulation of all these fibers produces rotatory movements. There is still no evidence as to whether this is also true for the fibers connecting the nucleus interstitialis to the nucleus niger and the supraoptic commissure of Ganser. Only the most medially located fibers of the brachium conjunctivum can produce slight head rotation following electrical stimulation, according to Hess & Akert (110). These fibers terminate partly in the nucleus ventro-oralis internus of the thalamus where they become connected with the efferent mechanism for rotation. These fibers originate in the medial cerebellar nuclei where Koella (152) in 1955 demonstrated rotatory movements with a technique similar to that of Hess. The nucleus interstitialis also receives afferent vestibulomesencephalic fibers from the ipsi- and contralateral side, partly originating in the nucleus vestibularis superior of von Bechterew. These rotatory effects are to be regarded physiologically as compensatory movements following rotatory stimuli, equivalent in effect to artificial electrical stimulation of the fiber connections of the nucleus interstitialis.

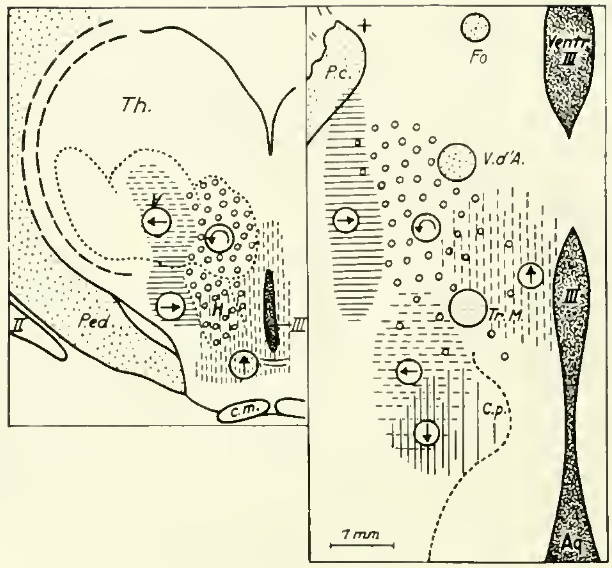

FIG. 9. Location in the cat diencephalon of points the stimulation of which produces direction-specific motor responses of the head and body. *Left:* Frontal section at the level of the posterior ventral nuclei (*V*) of the thalamus (*Th.*), H-fields (*H*) and corpus mammillare (*c.m.*). *Right:* Horizontal section showing the landmarks of the fornix (*Fo*), tract of Vicq d'Azyr (*V.d'A.*), tractus Meynert (*Tr.M.*) and posterior commissure (*C.p.*). The responsive areas are represented by *hatched lines*, *broken lines* or *circles*. The responses are indicated by symbols plotted in the center of the region from which they were evoked. Note the distribution of the fields with partial overlapping in horizontal and frontal planes. *Perpendicular hatching* indicates lowering; *perpendicular broken lines*, elevation; *circles*, rotation in the frontal planes; *horizontal hatching*, contraversive deviation in the horizontal plane; *horizontal broken lines*, ipsiversive deviation in the horizontal plane. [Redrawn after Hess *et al.* (111) and Hess (107).]

NEURONAL MECHANISMS OF UPWARD MOVEMENTS. Low-frequency threshold stimulation of the areas located medially and rostrally to the nucleus interstitialis (as shown in figs. 8 and 9) induces upward movements of the head and the anterior body which show synchrony with the stimulus frequency up to a rate of 8 per sec. Simultaneously the animal opens the eyelids, its pupils dilate, and the animal looks awake and slightly excited. If stronger stimuli are used, the contralateral shoulder and the forelimbs, but rarely the hind limbs, are involved. If the head is fixed, both eyes show conjugate vertical movements (87).

Coagulation of an area producing upward movements leads to a mirror-image defect: lowering of the head and anterior part of the body. Bilateral total destruction of the structures responsible for these movements produces a continuously lowered posture of the head, the chin leaning on the floor. Simultaneously there is also a loss of the ability to follow objects with the eyes in the vertical upward direction. Thus, it appears that the mechanism for upward movements is also tonically active during wakefulness. If there is an additional bilateral lesion in the dynamogenic zone of Hess in the posterior hypothalamus, the cats are drowsy, hardly react to environmental stimuli and do not correct uncomfortable postures.

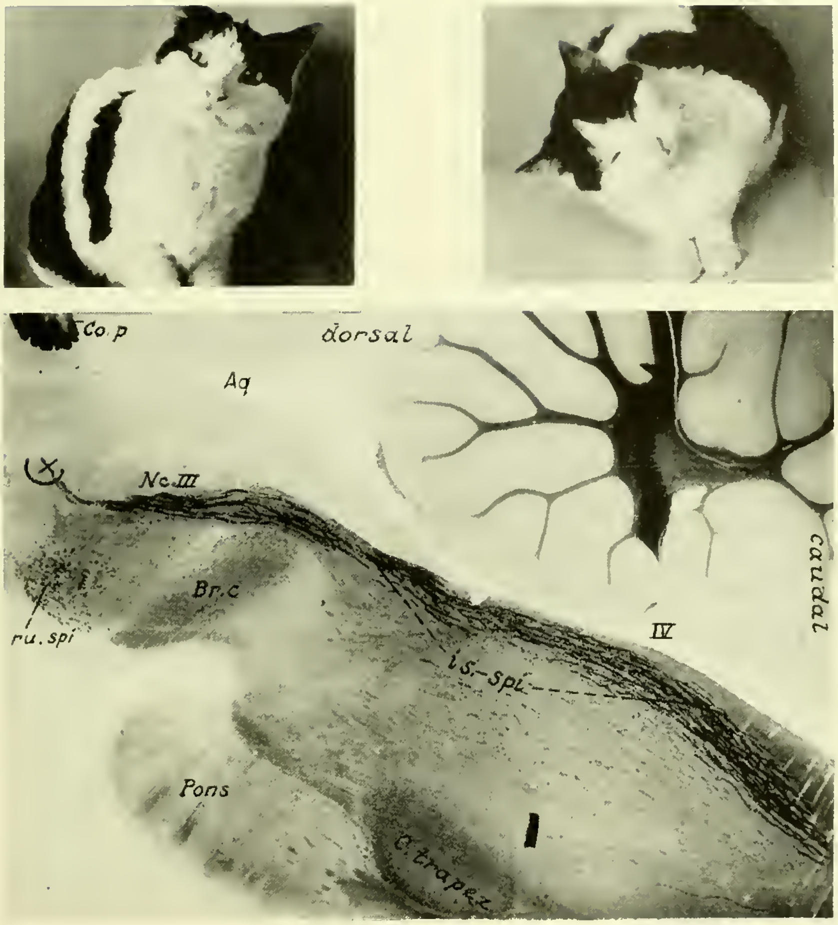

FIG. 10. Mirror-image effects on head position of stimulation and coagulation in the interstitial nucleus. *Upper left:* Stimulation (0.5 v., 8 per sec.) of the left interstitial nucleus causes rotation of the head to the left. *Upper right:* One day after coagulation at the stimulation point there appears a mirror-image rotation of the head to the right. *Lower:* The anatomical correlate of the rotated posture of the head is the degenerated interstitiospinal tract (*is. spi*). The stimulation point lies 0.5 mm more laterally. [From Hassler & Hess (91).]

The tonic coordinating mechanisms mediating upward movements are located in the ventroanterior mesencephalon dorsocaudally to the mammillary bodies and rostroventrally to nucleus interstitialis, according to Hassler (87). Their anatomical substrate is the nucleus prestitialis which is also called the nucleus interstitialis ventralis or inferomedialis (fig. 8). This nucleus has the following efferents which evoke more or less pure upward movements around the transverse axis on electrical stimulation: *a*) the descending fasciculus prestitiolongitudinalis found medially within the fasciculus longitudinalis medialis sending collaterals to all eye muscle nuclei and ending with a few thin fibers in the anterior horn of the cervical cord; *b*) the tractus tegmenti medialis, first described by Ogawa, which lies parallel to and slightly ventral to the fasciculus longitudinalis medialis and which sends its descending fibers down to the medial accessory olive, thus conveying impulses for upward movements to the cerebellum; *c*) the prestitiohypothalamic fibers passing rostrally through the hypothalamus along the external border of the central grey which convey impulses to hypothalamic mechanisms correlated with emotional reactions; and *d*) the prestitiorubral fibers going in a caudal direction to the anterior part of the nucleus ruber (see fig. 8). The efferent pathway of the nucleus ruber, the rubrospinal tract, produces raising of the head and anterior body when stimulated electrically, as shown by Hess & Weisschedel (112). This pathway provides the mechanisms for upward movements with a fast conducting descending pathway to the anterior horn system. In contrast to the nucleus prestitialis and its pathways, the tractus rubrospinalis is not maintained in tonic activity (87). Less conspicuous connections are also made from the nucleus prestitialis to the nucleus entopeduncularis and to the pallidum. These fibers connect the statokinetic systems with the extrapyramidal centers.

NEURONAL MECHANISMS OF DOWNWARD MOVEMENTS. Physiological investigation of the mesencephalon

in cats by means of electrical stimulation has demonstrated separate mechanisms responsible for downward movements of the head and anterior body (fig. 9); their rostral limit is located just in front of the posterior commissure according to Hess (106). The effects following low-frequency stimulation show synchrony with the stimulus frequency but slow recovery after each stimulus; thus a progressive lowering of the head and anterior body occurs until the cat touches the ground with its head. A few areas located very close to the mid-line, when stimulated, show behavioral depression of the animal in addition to the tilting effect.

The mechanism for downward movements is also tonically active. Its destruction produces an upward posture of the head with upward looking eyes. The cat than stalks around and lifts its feet unusually high. The defect is compensated after a few days.

The structure coordinating these movements is the nucleus precommissuralis (fig. 8) located immediately rostrally to the posterior commissure and dorsally to the aqueduct, according to Hassler (unpublished observations based on material in the Hess collection). Its efferent pathway is the tractus precommissurotegmentalis, corresponding to the thalamopretectotegmental tract of Bucher and Bürgi. The pathway follows the fasciculus longitudinalis medialis within its lateral area, sends collaterals to the nucleus nervi abducens and to the reticular formation of the medulla oblongata, and terminates in the area of the inferior olives. Only a few collaterals go rostrally to the caudal lamella medialis thalami which belongs to the hypnogenic zone of Hess.

NEURONAL MECHANISMS OF IPSIVERSIVE TURNING MOVEMENTS. Movements in the horizontal plane are coordinated by two separate systems: one for ipsiversive and the other for contraversive turning movements.

In freely moving animals ipsiversive movements can be induced by stimulation of the pontine and mesencephalic reticular formation. The often discussed so-called 'tegmental reaction' (of Thiele as well as of Ingram, Ranson and co-workers) is nothing but an ipsiversive movement distorted by anesthesia and by the fact that the animal is restrained [Bürgi (27), Hassler (89)]. This effect looks very much like the compensatory vestibular movements in the horizontal plane produced by Bartorelli and Wyss using rotational stimuli. In contrast to rotation, upward and downward movements, ipsiversive turning movements do not show synchrony with the stimulus frequency, even at frequencies as low as 8 per sec., but are continuous. Both onset and disappearance occur with a certain latency. The eyes do not precede in the direction of the movements.

The corresponding anatomical structure is a fiber bundle within the dorsolateral reticular formation, the vestibuloreticulothalamic tract [Hassler (89)]. This nondecussating pathway consists of the fasciculus tegmenti dorsolateralis and of its prolongation in the tegmental fascicles of Forel terminating in the nucleus ventrointermedius of the thalamus (see fig. 11). Many fibers end in the mesencephalic reticular formation and are replaced by new fibers. After removal of the cerebrum, ipsiversive turning movements can also be produced by stimulation of the exposed surface of the mesencephalon (Thiele) which activates descending reticular pathways. The sustained character of the movements results from the transmission of the impulses through a great number of reticular synapses before they reach the efferent reticulospinal pathways leading to the spinal cord. The highest destination of this pathway, the nucleus ventrointermedius thalami, projects to the region of the central gyri. Walzl & Mountcastle (290), Kempinski (143) and especially Mickle & Ades (191) were able to detect changes in electrical activity along this pathway following electrical or physiological vestibular stimulation. In cats the vestibular projection to the cortex is located in the anterior suprasylvian gyrus, corresponding to the inferior postcentral gyrus in primates. In human subjects Penfield & Rasmussen (209) stimulated the area of the central gyrus; the eye movement most frequently obtained was a conjugate lateral eye deviation to the ipsilateral side which is understandable on the basis of the existence of the above mentioned pathway. (In man eye movements are to a considerable extent independent of movements of the head and trunk.) Because of certain features of the nerve fiber systems involved, one of us (Hassler) considers area 3a, which contains giant pyramidal cells, as the central vestibulocortical projection.

NEURONAL MECHANISMS OF CONTRAVERSIVE TURNING MOVEMENTS. Contraversive turning movements are much more varied in their physiological characteristics and anatomical substrates than those just described. The adversive movements following stimulation of many extrapyramidal cortical areas also belong to this group. Such movements generally occur after a short latency but occur continuously, even at

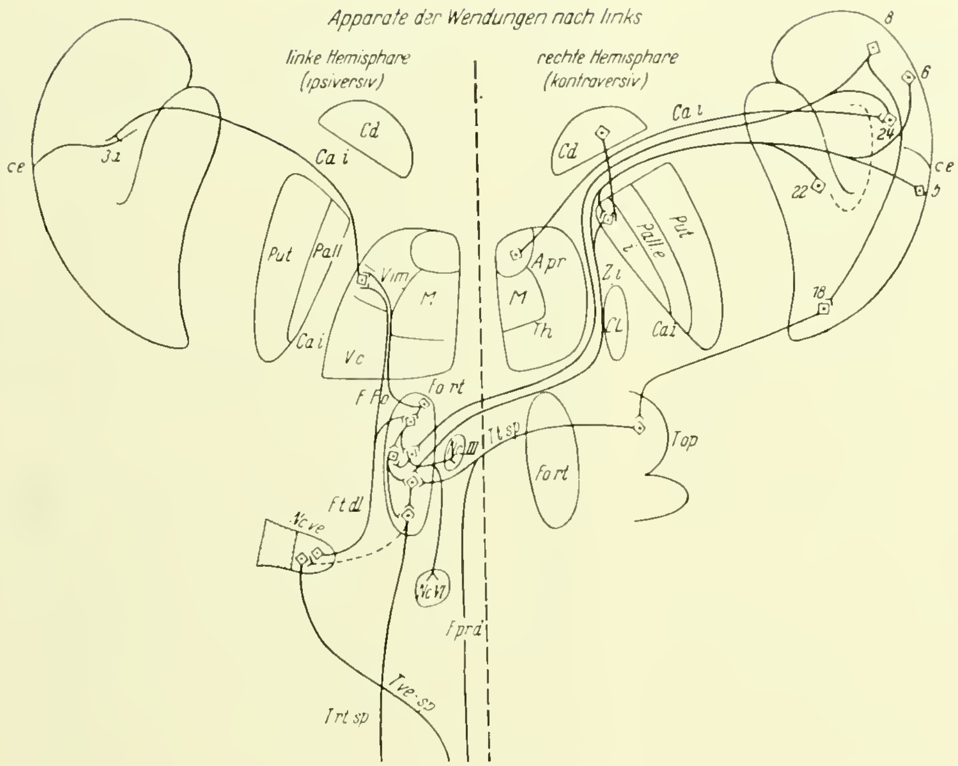

FIG. 11. Neuronal mechanism for turning movements in the horizontal plane to the left side. The apparatus for ipsiversive turning is schematically drawn on the *left* of the figure, that of contraversive turning on the *right*. From the vestibular nuclei (*Nc.ve*) arises the ipsilateral vestibuloreticulothalamic tract which is called the dorsolateral tegmental fascicle (*F.t.dl*) in its first part and, more rostrally, Forel's tegmental fascicles (*F.Fo*). The fibers of this fascicle terminate in the ventrointermediate nucleus of the thalamus (*V.im*). From there arise the cortical projections to the central region, probably area *3a*. One of the contraversive turning systems starts from the anterior thalamic nucleus (*A.pr*) and reaches area *24* of the gyrus cinguli. This area and all adversive cortical areas (*8, 6, 5, 22*) send fibers through the internal capsule (*Ca.i*) to the entopeduncular nucleus (*Pall.i*). This nucleus also receives fibers from the caudate nucleus (*Cd*). The efferent tract runs through the zona incerta (*Z.i*) near the subthalamic nucleus and crosses the mid-line in the anterior midbrain. It is connected with the reticular formation which contains the apparatus for all turning movements to the same side. Its efferent tract is mainly the reticulospinal tract (*T.rt.sp*). Another pathway for contraversive movements arises in area *18* and passes through the tectum opticum (*T.op*) where it is connected with the substrate of optic grasp reaction. The efferent path, the tectospinal tract (*T.t.sp*) also mediates contraversive turning. It crosses the mid-line and descends as the predorsal fascicle (*F.pr.d*). [From Hassler (89).]

stimulus frequencies below 10 per sec. The eye movements precede the body turning in the same direction. Stimulation of many areas simultaneously produces a dilatation of the pupils. Contraversive turning movements easily merge into circling movements. The latter have been described above as related also to the caudate nucleus. The conjugate eye movements produced by stimulation of the tectum opticum, also called visual grasp reactions (Akert and Hess), rarely turn into circling movements. Following stimulation of the cingulate gyrus the body and head follow the movements of the eyes to the contralateral side only after some time. In man these contraversive movements are almost completely restricted to the eyes. Such a *déviation conjuguée* can be shown experimentally in an *encéphale isolé* preparation in which movements of the trunk and limbs are impossible [Hyde & Eliasson (124, 125)]. In unrestrained cats passive holding of the head may be sufficient to induce an isolated conjugate movement

of the eyes instead of the turning movement of the head.

The mechanisms for turning movements (contra- and ipsiversive) again show tonic activity. Their destruction is followed by a tendency to circling movements in the direction opposite to the effect of stimulation, that is in contraversive direction following destruction of the ipsiversive structures and in ipsiversive direction following destruction of the contraversive substrate. The perception of sensory stimuli contralateral to the direction of circling following operation may be considerably impaired or even abolished [Hess (103, 104)]. This effect corresponds to the hemianopic impairment of attention and to the results of destruction of the frontal eye fields in human pathology. If the destructon is not too extensive, the horizontal circling movements disappear after a few days.

The neuronal systems responsible for these movements are manifold and, as a result of the length of their fibers, can be found in many areas of the brain. The nucleus caudatus, the nucleus entopeduncularis, the zona incerta and its caudal efferent fibers all contain substrates for contraversive turning movements [Hassler (89)]. It is probable that these areas also are connected in part with the efferent pathways originating in the cortical fields responsible for adversive movements. These pathways and their possible interrelation are shown schematically in figure 11. In any case, there is in the anterior mesencephalon a connection between these neuronal systems and the reticular mechanisms responsible for ipsiversive turning movements. The fibers responsible for conjugate deviation of the eyes to the contralateral side seem to cross the mid-line at a higher level. A common 'selecting organ' (Hess) for all turning movements to the ipsilateral side seems to exist in the mesencephalic reticular formation, as shown in figure 11.

Cortical Extrapyramidal Areas in Relation to Subcortical Extrapyramidal Centers

The functional relationship between the cortical areas and the subcortical extrapyramidal structures requires discussion. In animals stimulation of some areas of the cortex can induce motor reactions even though the pyramidal tract has been severed in the medulla, as Starlinger (245) first showed in dogs. His observations were confirmed later by Prus (214), Rothmann (221), Vogt & Vogt (267), Tower (255) and others. These areas were accordingly called extrapyramidal motor cortical fields. By electrical stimulation, Vogt & Vogt (267) distinguished from area 4, the primary motor field, a secondary field, area 6, where stimulation also produced selective movements which in contrast to those evoked from area 4 are less sharply localized and are accompanied by adversive movements to the contralateral side. Later (268) these workers described the responses to stimulation of many other cortical areas, including a tertiary motor field in the frontal cortex (area $6a\beta$), various areas producing adversive movements, and a peculiar inhibitory area for rhythmical chewing and licking movements (area 8γ). Foerster (58) obtained the same results in human subjects.

Destruction of area 6 as a whole causes 'forced grasping.' This first appears as 'coarse grasp reflex' [Seyffarth & Denny-Brown (232)] which can be produced by strong pressure applied to the palm and appears as a reflex contraction of the flexor muscles of the fingers. This effect later turns into a true grasp reflex which is eliminated by complete deafferentation. Finally, the 'instinctive grasp reaction' appears which consists of movements of orientation of the hand produced by contacting any place of the palm. According to Denny-Brown (41) the grasp reaction is permanently released only following combined destruction of the cingulate gyrus, the supplementary motor area and area 8. If only parts of these areas are destroyed, the grasp reactions disappear later. Simultaneously with the appearance of the grasp reactions there is a loss of the 'avoiding reaction' (42).

Bilateral destruction of areas 4 and 6 produces the so-called 'thalamic reflex pattern,' so named because of its similarity to the motor reactions of the decorticate (thalamic) monkey. In this preparation all postural and locomotor reactions remain unimpaired. However, directed motor activity is dominated by the grasp reactions. If the animal lies on its side the grasp reactions of the extremities lying underneath are decreased while those of the extremities of the upper side are enhanced. Simultaneously the flexor reflexes are exaggerated and the head is kept elevated [Fulton & Dow (65)]. Tonic neck reflexes are consistently present only if the ventral part of area 4 and 6a, including area $6b\alpha$, has also been removed. Additional bilateral destruction of the labyrinth restores the normal posture of the head and decreases the strength of the neck reflexes and all postural reactions including the grasp reflexes. Following head rotation these animals extend the 'jaw' limbs and flex the 'skull' limbs and simultaneously show an enhanced grasp reflex. Thus, the

grasp reflexes are always particularly pronounced in the flexed extremities. A spastic increase of muscle tone is often, but not always, combined with the forced grasping. A kinetic apraxia of the limbs may occur in man along with grasp reactions following lesions of area 6.

Stimulation of area 4s (the strip region of Hines) produces relaxation of hypertonic muscles or voluntary contractions in the contralateral extremities or a slow tonic movement of the ipsilateral fingers, elbow and shoulder [Wyss (298)]. According to Bucy & Fulton (26), these ipsilateral effects are not mediated in the spinal cord by the pyramidal tract. Destruction of area 4s produces a transitory spastic paralysis which can be enhanced by lesions in area 6 or area 4. McCulloch *et al.* (179) were able to demonstrate a pathway from area 4s to the medial reticular formation of the medulla from which the impulses were conveyed to the spinal cord through reticulospinal fibers. These findings are in keeping with Wagley's observations (283) that interruption of the lateral or ventral reticulospinal tract, in addition to the pyramidal tract, is necessary for the appearance of a spastic increase of muscle tone. The inhibitory fibers of the medial reticular formation reach certain interneurons of the anterior horn.

Connections of area 4s with the caudate nucleus were found with the strychnine method, but could not be confirmed by the Marchi method [Verhaart & Kennard (265)]. The suppressor effects of area 4s, apparently demonstrated in older experiments, have been largely refuted; this is, however, not true for the motor effects of stimulation described here. According to the investigations of Travis (257), spastic hypertonus following cortical lesions in the macaque appears only if the supplementary motor area is removed in addition to the precentral motor area. As the corticofugal projections of the supplementary motor area enter the cortical white matter rostrally to the efferents of the precentral motor area, they probably were interrupted in the white matter in earlier experiments in which extensive lesions of area 4s were produced. This would explain the spasticity occuring after these lesions.

The anatomical and electrophysiological topography of area 6 was first studied by Vogt & Vogt (268). The part having no giant pyramidal cells, located immediately rostrally to area 4γ, is called area 6aα; in front of this area and covering the convexity and the medial surface of the brain they differentiated area 6aβ, and in addition areas 6bα and 6bβ located at the lower end of the central gyrus. Later Hines (113–115) separated the strip region (area 4s) from the frontal border of area 6aα. Area 8 of Brodmann, which has a very thin fourth layer, constitutes the transition to the granular prefrontal cortex.

Faradic stimulation of area 6aα produces tonic isolated movements mostly of the large proximal joints of the contralateral extremities, with a tendency to involve the other joints of this limb and of the other limb of the same side. The ipsilateral limbs are also involved and sometimes even first [Bucy & Fulton's ipsilateral representation (26)]. The threshold is higher and the responses have a longer latency than those obtained from area 4 and they outlast the stimulus for a longer time. The safety margin for epileptic seizure activity is much smaller and barbiturate anesthesia more easily blocks the responses to stimulation of area 6aα. If stronger stimuli are used, an adversive movement of the whole body to the opposite side appears in addition to the tonic isolated movement. The tonic isolated movement is mediated by area 4, whereas the adversive movement is produced by direct projections to the brain stem [Vogt & Vogt (268)]. Stimulation of the face area of area 6aα produces complex movements of groups of facial muscles due to excitation of the adjacent area 4 [Walker & Green (287)].

Area 6aβ [Vogt & Vogt (268)], when stimulated with threshold stimuli, gives rise to adversive movements mediated by direct efferent fibers. In monkeys this is true both for the areas covering the convexity and the medial surface of the brain. Stronger stimuli produce additional tonic isolated movements, considered to result from propagated excitation of area 4. Lesions of area 6aβ are followed by the appearance of a grasp reflex without spasticity.

Stimulation of area 6bα even with weak currents produces rhythmical movements of the mouth and the lips, chewing and swallowing movements as well as salivation [Vogt & Vogt (268)]. These effects are mediated by direct efferent paths and remain unimpaired after removal of area 4.

Weak stimulation of area 6bβ and of its dorsal continuation in area 8γ elicits inhibition of respiration or of the rhythmic chewing, swallowing, mouth and respiratory movements which can be obtained by stimulation of area 6bα. These movements are mediated by direct centrifugal pathways. Stronger stimuli also produce adversive movements [Vogt & Vogt (268)]. Stimulation of area 8 produces opening of the eyelids and conjugate lateral movement of the eyes sometimes with turning of the head to the op-

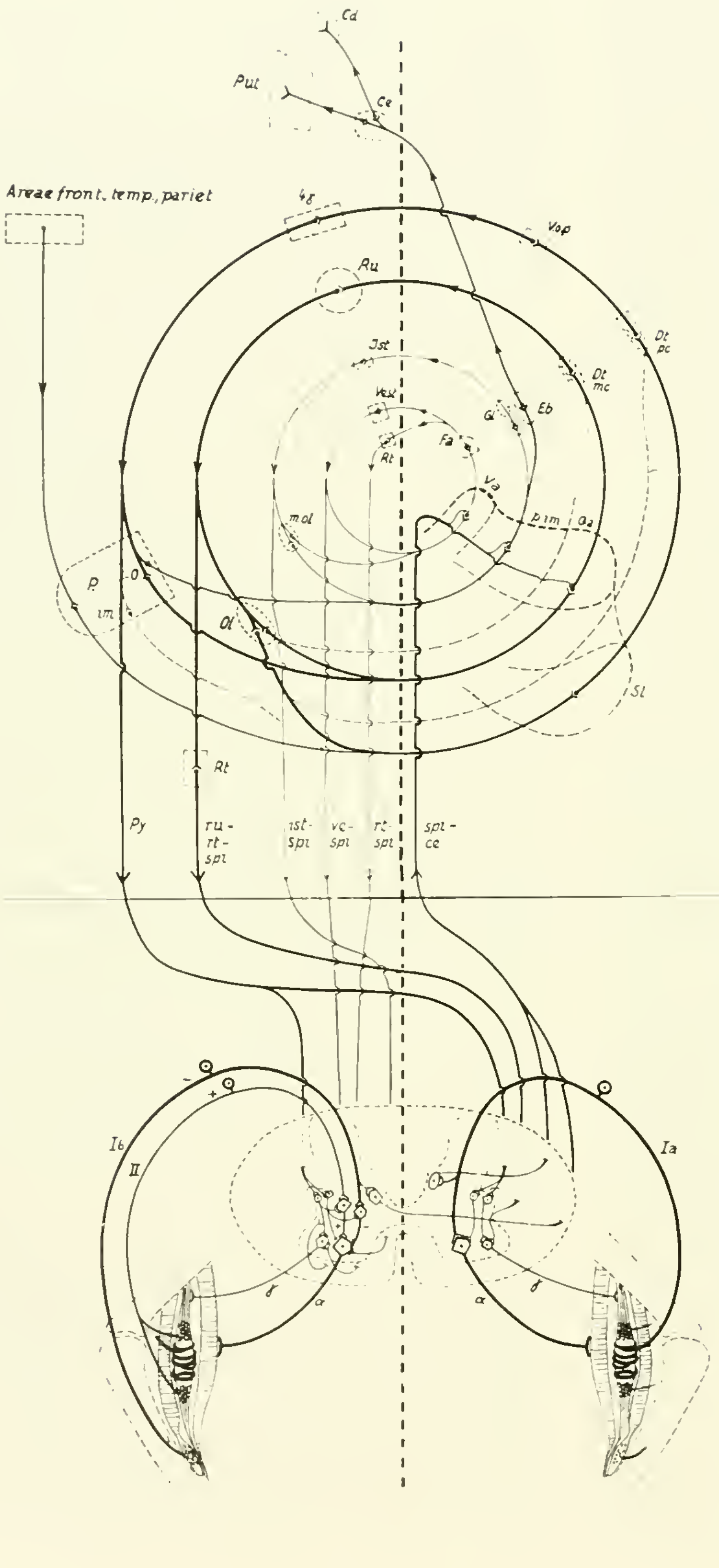

FIG. 12. Neuronal chains of the central motor systems, showing the relation of the lower extrapyramidal structures with the cerebellum, the cerebral cortex and the spinal servomechanisms.

Upper part. The schematic drawing shows on the *right side* the cerebellum with its spinal afferent pathways, the spinocerebellar tracts (*spi.-ce*), to the three longitudinal zones of the anterior cerebellar lobe. Impulses arising in integrating cortical areas (*areae front., temp., pariet.*) pass through corticopontine tracts and intermediate pontine nuclei (*P.im*) to the semilunar lobe (*Sl*) of the cerebellar hemispheres. From there they run through the parvicellular part of the dentate nucleus (*Dt.pc*) and the dentatothalamic fibers to the posterior ventral oral nucleus of the thalamus (*V.o.p*) and to area 4 of the cerebral cortex (*4γ*). The large fibers of the pyramidal tract originating in area 4 send collaterals to the oral pontine nuclei (*P.o.*). There a multineuronal reverberating circuit starts to the lateral or quadrangular part of the anterior cerebellar lobe (*Qa*), leading through the magnocellular dentate nucleus (*Dt.mc*) to the red nucleus (*Ru*). Thus the pyramidal impulses coordinate cerebellar and rubral control systems with the reticular formation and spinal cord. After one loop through the cerebellum to the motor cortex is passed, another circuit goes through the red nucleus and the central tegmental tract to the inferior olive (*Ol*) leading back to the quadrangular anterior lobule, so closing the self-controlling circuit of the pyramidal system starting in the semilunar lobe of cerebellum. From the oral pontine nuclei (*P.o*) start two other neuronal chains over the intermediate part of the anterior cerebellar lobe (*p.im*). The first goes through the emboliform nucleus (*Eb*) and the centrum medianum (*Ce*) to the caudatum (*Cd*) and putamen (*Put*). The continuation of this first neuronal chain is omitted because it spares the cerebellum. The second chain passes from the intermediate part of the anterior lobe through the globose nucleus (*Gl*) to the substrate for rotation in the nucleus interstitialis (*Ist*). Its main efferent pathway is the interstitiospinal tract (*ist-spi*) to the anterior horns. This postural pathway has also a self-controlling circuit via the medial tegmental tract, the medial accessory olive (*m.ol*) to the intermediate part of anterior lobe near the vermis anterior (*V.a*). From *V.a.*, fibers arise to the vestibular nuclei (*Vest*) and to the reticular formation (*Rt*) of the brain stem. The efferent pathways are the vestibulospinal and reticulospinal tracts (*ve.-spi* and *rt.-spi*). All efferent fiber tracts reach the interneuron pool of the anterior horns. In the spinal cord extrapyramidal impulses do not excite the motoneurons directly but probably end in interneurons influencing the external servomechanisms of muscle length and muscle tension or fire gamma neurons to the intrafusal muscle fibers of muscle spindles.

Lower right. Spinal servomechanism regulating muscle length. The receptors are the annulospinal

posite side. Removal of area 8 is followed by a transitory loss of attention and an impairment of response to all stimuli from the opposite side, a state resembling the hemianopic impairment of attention in human disorders called 'unilateral neglect' by Welch & Stuteville (292). There is, furthermore, a paralysis of conjugate horizontal movement of the eyes to the side of the lesion and occasionally forced circling of the animals in the same direction. Bilateral resection of area 8 produces a bilateral restriction of the visual fields and increased motor activity with almost continuous locomotor movements [Kennard *et al.* (147)].

Localized stimulation of the postcentral gyrus (areas 3, 1 and 2) is followed by reflex twitching of those parts of the body having their sensory representation in the stimulated area. The motor effect is due to propagation of the stimulus and excitation of the motor representation located approximately at the same level in the precentral gyrus. Lesions of these areas 3, 1 and 2 do not cause any marked motor impairment; a permanent hypotonia of the muscles appears but voluntary motor activity is fully restored. Simultaneously the contralateral proprioceptive reflexes are slightly enhanced. The hypotonic central paralysis rapidly produces a contralateral muscular atrophy which almost never occurs following precentral lesions in spite of stronger impairment of voluntary motor activity.

In man the responses to stimulation of the extrapyramidal cortex are still problematical, but Foerster (58) found responses of the different cortical areas to be very similar to those described by Vogt & Vogt in the monkey. Penfield and co-workers later studied the differentiation of the precentral cortex in greater detail; they however failed to distinguish between pyramidal and extrapyramidal fields. The delimitation of the motor area toward the frontal pole has not been clearly established. The speech arrest and vocalization fields and, in particular, the motor supplementary field located on the medial side of the hemisphere with its somatotopic organization were added to the picture. Vogt's map of cortical stimulation designates the latter field as part of area 6aβ. In the newest maps of cortical stimulation prepared by Penfield & Jasper (208) there is no comment whatsoever on the problem of the extrapyramidal cortical areas and their functions.

Responses to stimulation during subcortical operations on the thalamic nuclei projecting to area 4, 6 and 8 closely resemble the responses of the corresponding cortical areas as would be expected on the basis of the very close functional and anatomical interrelationship between these structures.

The resection of parts of area 6 by Horsley was the beginning of the modern surgical therapy of hyperkinesia. The physiological significance of this observation has been discussed above (p. 877).

Extrapyramidal Efferent Mechanisms and Their Interrelations with Cortical and Cerebellar Systems

The parts of the extrapyramidal motor system least well known are the efferent mechanisms. Their functional role is understandable only on the basis of an overall analysis of motor mechanisms in relation to the cerebral cortex and the cerebellum.

Within the organization of the motor system there is a highest level above that of the precentral motor cortex which makes possible cortical teleokinetic activity (see p. 903). This 'psychomotor' level is located in primates in the so-called association areas of the frontal and temporal lobes and possibly also in the integration areas of the parieto-occipital cortex. Impulses for extrapyramidal associated movements and for readiness of the peripheral motor system—probably mediated by the gamma neurons of the anterior horn—can be initiated over connections between these prefrontal and parietotemporo-occipital areas and the nucleus niger (via the tractus prefrontonigralis and temporoparietonigralis). As we know, the intention of moving or its imagination produces an increase of muscular tone under normal conditions and may even evoke involuntary movements or spasms in patients with hyperkinetic disorders and serious pyramidal lesions. A pathway from the nucleus niger to the internal pallidum simultaneously changes the excitability of the premotor cortex (areas 6aα, '4s' and 6aβ). These prefrontal and parieto-occipital association areas have particularly important connections with the pontine

endings of the muscle spindles. They send *Ia* afferents to the posterior root and send reflex collaterals directly to the alpha motoneurons (α). This regulating circuit can be shifted to higher sensitivity by gamma innervation of the intrafusal muscle fibers of the muscle spindle. When no central innervation by gamma neurons is available, this servomechanism regulating length is interrupted.

Lower left. Spinal servomechanism regulating muscle tension. This mechanism has facilitatory receptors in the flower-spray endings and an inhibitory receptor in the Golgi tendon organs. Their centripetal fibers, the *Ib* and *II* afferents in the posterior roots, influence the motoneurons by chains of interneurons. This tension circuit can also be shifted to higher sensitivity by gamma innervation. [Redrawn from Hassler (88).]

central grey via the frontopontine (Arnold) and parietotemporopontine bundles (Türck). An afferent control circuit involving the cerebellum becomes effective in regulating voluntary movements by means of these very numerous corticopontine connections—especially in primates and in man—the fibers of which are much more numerous even in the macaque than are the fibers of the pyramidal tract [Verhaart (263, 264)]. As shown in figure 12 this circuit goes back to the cortex since the nuclei pontis intermedii are closely connected with the neocerebellar hemispheres which cooperate intimately with the motor cortex, particularly by excitation of area 4γ, the principal site of origin of the largest fibers of the pyramidal tract. The neocerebellum projects to area 4γ via the brachium conjunctivum and the nucleus ventro-oralis posterior thalami (V.o.p.). The existence of this neuronal link has also been confirmed electrophysiologically by Walker (285).

Thus, by means of the detour over the cerebellar hemispheres, the psychomotor cortical areas can stimulate the precentral area responsible for voluntary motor activity. Simultaneously there is a possibility that niger impulses initiated by the activity of the psychomotor cortical areas may be conveyed to the peripheral motor system. Indeed, the impulses destined for the motoneurons and originating in the cortical regions giving rise to the pyramidal tracts do not travel via the pyramids alone. As Lloyd (165) has shown, the impulses traveling in the pyramidal tract are preceded by impulses conducted by long reticulospinal and propriospinal fibers. These impulses activate the interneurons and probably also the motoneurons of the anterior horn. The pyramidal fibers themselves do not usually connect directly with the motoneurons but first induce firing of interneurons which in their turn influence the excitability of the motoneurons or of spinal synapses of the peripheral mechanisms controlling muscular tone or length (the external loops of fig. 12).

Some of the impulses from area 4γ go via corticopontine or collateral fibers to the oral pontine ganglia from which they may proceed to the lateral part of the cerebellar anterior lobe (lobulus quadrangularis anterior). This structure is responsible for integration of pyramidal impulses with impulses from the muscle and tendon receptors and probably also from other exteroceptive and vestibular sources. The results of this coordinative activity are communicated to the nucleus ruber via the nucleus dentatus magnocellularis, according to Hassler (83), and eventually reach the motor cortex, so completing a feed-back circuit.

In its turn, the nucleus ruber regulates the excitability of the interneuronal mechanisms of the anterior horn and of the gamma cells via the rubrospinal tract and rubroreticulospinal fibers, its integrating cerebellofugal impulses with others originating in the precentral cortex, the pallidum and the systems regulating statokinetic activity and locomotion. Another feed-back system originates in the nucleus ruber, the central tegmental pathway to the inferior olives. These structures, in which the feed-back impulses are coordinated with impulses from the anterior columns of the spinal cord, project to all areas of the cerebellar cortex, including to the lobulus quadrangularis anterior which, as noted above, is the origin of afferent impulses to the nucleus ruber. In this way a multineuronal feed-back circuit which controls the ruber activity in part by means of its own impulses is closed.

Not only are the cortical and rubral efferent motor systems provided with such feed-back mechanisms but so is the striatum itself (the cerebelloembolocentrostriatal neuronal chain shown in fig. 12). The intermediate zone of the anterior cerebellar lobe where the spinocerebellar impulses from the muscle receptors are coordinated with those from the motor cortex is provided with a sort of 'efferent copy' (von Holst) through the feed-back systems from area 4γ reaching it via the oral pontine ganglia. These integrated impulses are projected from the intermediate zone of the cerebellar anterior lobe via the nucleus emboliformis and the centromedian nucleus to the putamen and caudate nucleus.

These extrapyramidal centers convey their impulses through the internal and external pallidum and nucleus ventro-oralis anterior of the thalamus (V.o.a.) to area 6aα, area 6aβ and the supplementary motor area following manifold coordination with impulses from other structures. These cortical areas also communicate the pattern of their efferent impulses via the oral pontine ganglia to the lateral zone of the anterior cerebellar lobe and in part also back to putamen, caudate nucleus or pallidum (88). Thus it appears that each efferent motor system is provided with such a self-regulating feed-back mechanism.

Further, impulses from the intermediate zone of the anterior cerebellar lobe proceed via the nuclei globosi to the statokinetic systems of the mesencephalon: the nuclei interstitialis, prestitialis and precommissuralis. These mechanisms controlling posture

and locomotor activity, in addition to their efferent impulses to the peripheral motor system, give rise to a feed-back circuit via the medial tegmental tract of Ogawa to the medial accessory olives and thence back to the pars intermedia of the anterior cerebellar lobe and to the vermis anterior. The latter is a collecting area for information which is coordinated and then conveyed via the nucleus fastigii to the vestibular nuclei and to the reticular formation. The vestibular nuclei again are provided with a self-regulating mechanism over vestibulocerebellar fibers projecting especially to the vermis. The mesencephalic reticular formation is moreover the common control organ for horizontal turning movements to the ipsilateral side and is also a collecting area for impulses of very heterogeneous origins.

Feedback for regulation of intrinsic activity and that of other motor systems seems to be a general principle of all motor systems. Each system is capable of taking into account, for its later activity, modifications in the peripheral motor situation induced by its proper influence and also of coordinating these modifications with information concerning the innervation and resistance in the periphery and with impulses from other systems.

However, this intrinsic and coordinative regulatory activity within the central motor systems does not seem able to cope with all the possible perturbations of peripheral motor activity. Another coordinative process occurs at the spinal segmental level. Here the direct corticospinal or other long fiber systems in general have no direct connections with the motoneurons. Reticulospinal and propriospinal fibers are interposed between the extrapyramidal centers and the anterior horn system, while Lloyd (165) was able to demonstrate electrophysiologically the lack of effect of the direct bulbospinal fibers on motor mechanisms. The large number of afferents ending on the anterior horn interneurons and the motoneurons definitely suggests that the question whether the central impulses can produce their destined effect within the peripheral motor system at a certain moment is once more raised and checked in the anterior horn itself. The interneuronal system of the anterior horn is also responsible for the first control and checking of the afferent impulses from the muscles which ordinarily tend to elicit motor impulses. Furthermore, the firing of both the alpha and gamma motoneurons is constantly controlled peripherally by the mechanisms regulating muscle tension and length, in close correlation with proprioceptive and possibly also with other as yet unknown peripheral control mechanisms.

The various pyramidal and extrapyramidal impulses integrated in the self-regulating circuits described above are conveyed to the anterior horn by the following pathways: tractus reticulospinalis lateralis and ventralis, tractus rubrospinalis, tractus vestibulospinalis, tractus interstitiospinalis, tractus prestitiospinalis and descending nigrospinal fibers, occasionally interrupted in certain areas of the reticular formation.

PHYSIOLOGICAL CORRELATIONS AND FUNCTIONAL SIGNIFICANCE

In the foregoing portion of this chapter the experimental and clinical findings relative to the various extrapyramidal structures have been reviewed in an effort to identify specific functions for each nucleus.

However, only in the case of the directional mesodiencephalic responses described by Hess in the cat does the localization of the morphological substrates and efferent pathways seem certain enough to provide a useful model for study of extrapyramidal motor performances. No other functions can yet be defined in physiological and morphological terms. It seems to be certain only that the extrapyramidal motor system contains many neuronal chains and self-regulating mechanisms with positive and negative feedback, and that close coordination with the corticospinal system of the motor cortex and with the cerebellum is the main condition for normal extrapyramidal function, this relation becoming increasingly important in the higher forms, especially in monkeys and man.

Leaving now an essentially anatomical approach, we will in the following discuss from a physiological viewpoint the activities of the extrapyramidal system in relation to posture and locomotion, spinal reflexes, the thalamoreticular system, instinctive behavior and some aspects of the electrical activity of the brain.

Role in Posture and Locomotion

An important function of the extrapyramidal motor system is the regulation of posture. The mechanisms of postural regulation are localized mostly in the lower brain stem as they involve close coordination with the cerebellum and vestibular apparatus.

POSTURAL MECHANISMS AS CONCEIVED BY MAGNUS SCHOOL; OPTOVESTIBULAR REGULATION. Magnus' book

(173) on body posture summarizes the pioneer work done by himself and his school together with the old literature. The tonic reflexes of the head and trunk induced by proprioceptive afferents from the neck and the otolithic apparatus of the labyrinth were found to be represented in the rhombencephalon and upper cervical cord. The righting reflexes (*Stellreflexe*) were regulated by pontine and mesencephalic centers. However, Magnus and Rademaker's conception that normal body posture is the result of an equilibrium of reflexes is certainly too narrow and its experimental basis obtained by brain-stem transections at different levels in rabbits seems insecure. It must be supplemented by Hess' experiments on *richtungsspezifische* motor responses after diencephalic and mesencephalic stimulation in cats, by observations of behavior of different animal species and by clinical observations of extrapyramidal motor mechanisms in man. Magnus overrates the reflex conception of peripheral regulation mechanisms from labyrinthine and muscular receptors and neglects the spontaneous innate coordinative activity of the central nervous system, both of which work together to assure body posture.

The equilibrium of different 'forces' that assures normal body posture is not an equilibrium of reflexes as Magnus conceived it but a central order of coordinated self-regulation of several brain-stem centers that may be modulated by receptor and reflex mechanisms with positive and negative feedback. Magnus arrived at his conclusion mainly from experiments in rabbits, a species in which labyrinthine afferents are more important for body posture than in other species. Therefore, Rademaker preferred dogs for his experiments on cerebellar functions and Hess used cats for his stimulation experiments. The extrapyramidal functions of man and of these different species cannot be homologized. But in spite of the marked species differences some general conclusions on the regulation of body posture can be drawn. Although Rademaker's claim that the labyrinthine and body-righting reflexes were localized in the red nucleus was not confirmed by the localized rubral lesions produced by Mussen (198), localization of these mechanisms above the pontine level is generally accepted. Several structures in the mesencephalic tegmentum and tectum and in diencephalic subthalamic nuclei are the main regulators of body posture. Their identification with certain nuclei and tracts of the brain stem was made possible by Hess' studies involving stimulation and coagulation in the mesodiencephalon (described in the preceding section on statokinetic structures in the brain stem).

Optovestibular regulations are basic to orientation in space and are the essential sensory basis of postural mechanisms. Among the sense organs concerned, the eye contains the main exteroceptive and the labyrinth the main proprioceptive receptor organs for brain-stem posture regulations. Special adjustments of posture are mediated partly at the spinal level by receptors from muscles, joints and skin. The central substratum of optovestibular regulations is the lower part of the extrapyramidal motor system which coordinates afferent impulses from the eye and the labyrinth. The main integrating apparatus is the reticular formation of the pons and mesencephalon [Lorente de Nó (166, 167), Jung (134)] and some mesodiencephalic nuclei [Hess & Weisschedel (112), Hassler & Hess (91)]. The red nucleus is a specialized part of this reticular coordinating system differentiated for receiving cerebellar impulses.

The motor effects of the optovestibular system can be seen in all striated muscles of the body, but those on the ocular muscles are the easiest to record and to measure quantitatively and are also less complicated by the peripheral regulation of limb posture. The vestibular apparatus with its three semicircular canals represents the three planes of space; correspondingly, the eye is moved by three pairs of muscles in these planes. Between the labyrinthine receptors and eye muscle effectors a complicated coordinating apparatus is interposed. This integrating apparatus of the reticular formation modulates the impulses from the labyrinth and coordinates them with messages coming from the retina and other sense organs. The optovestibular functions resulting in eye movements and nystagmus have been described more fully elsewhere [Jung (134)]. Not only the stability of posture but also the effectiveness of perception during movements of the eye and the body (*Konstanz der Sehdinge*) is the result of fine regulation of the optovestibular system. This system uses a servomechanism coordinating afferent and reafferent messages with intracentral traces of efferent impulses, as shown by von Holst (280). The action of vestibular receptors on eye muscle innervation was recently summarized by Szentágothai (251).

HESS' EXPERIMENTS ON STATOKINETIC REGULATION AND THEIR DYNAMIC INTERPRETATION IN TERMS OF TELEOKINETIC AND EREISMATIC MOTILITY. The anatomical correlates of the brain-stem mechanisms for direction-

specific movements studied by Hess (100–105) were described earlier in the section on statokinetic structures in the brain stem. Only their principal features may be briefly reviewed here. Electric stimulation with implanted electrodes demonstrated the existence of a system of motor mechanisms in the mesodiencephalic regions of the extrapyramidal system controlling the position of the eyes, the head and the trunk (figs. 8, 11). Subsequent coagulation produced a mirror image of the pattern previously produced by stimulation of the same structures, as shown in figure 10. These observations indicate that posture is regulated by constant tonic activity of several antagonistic mechanisms operating in all three dimensions. Elimination of one of these mechanisms uncovers the activity of the antagonistic mechanism, normally in balance with it. Thus normal posture is the result of a dynamic equilibrium of central antagonistic forces continuously active in the waking state and controlled by peripheral afferents.

Hess has emphasized that intentional movements of the body are directed toward certain aims (*Erfolgsbezogen*). To reach these aims a characteristic posture and starting position of the body must necessarily be assumed.

"In the course of voluntary movements in consequence of muscular action there result certain reactive forces which are compensated, the governing impulses being supplied mainly by vestibular and proprioceptive mechanisms. These reflex preparations of start-positions provide what may be called the 'dynamic support' upon which the voluntary aimed movements are superimposed. In this functional conception no differentiation is made between pyramidal and extrapyramidal innervation, since these terms refer to anatomic relations. In order to emphasize the dynamic situation, the term teleokinetic (*telos* = aim) is used for the voluntary directed phase of the motion; and the term ereismatic (*ereisma* = support) is used to designate the other phase, which provides the basic conditions for every accurately aimed motion" [Hess (107)].

Figure 13 illustrates the action of the teleokinetic and ereismatic mechanisms in a model experiment in which three persons represent action and reaction of a motor performance. The intentional teleokinetic mechanism is represented by the upper person leaping to the point marked by the arrow. The supporting ereismatic mechanisms are represented by the second person carrying the leaper and providing postural mechanisms of support in anticipatory readiness for action, and by the third person supporting the second to compensate for the rebound. In the left row it is shown that all goes well for the intended movement when the ereismatic mechanisms give the right support and the supporting persons know when the upper jumps; the leaper reaches exactly the intended point. The right row shows the same leap made by the upper person but without proper preparation and supporting activity by the others. In this case the carrier falls backwards by the recoil of the leap and is caught only in the last moment by the third. The leaper jumps too short and falls because appropriate postural support is lacking and the proprioceptive reflex regulation of the second person comes too late to compensate for the recoil.

This model demonstrates some general principles applicable to ereismatic supporting actions in the motor system. Because the second and third men must 'feel' the weight and pressure of the first, 'know' the moment of the leap and continuously 'adapt' to various alterations of posture, the following three points are evident: *a*) proprioceptive reflexes of muscle and labyrinthine origin may be important parts of supporting regulation but act too late to compensate for unforeseen reactions of recoil; *b*) anticipatory activation of the proprioceptive control of supporting action therefore is necessary for effective motor performances and involves central activation of proprioceptive reflexes; and *c*) continuous self-regulating modification of postural support by higher central mechanisms compensating each other is needed for successful integration of voluntary movements. Although the conception of ereismatic innervation may seem to be purely theoretical, it indicates the existence of physiological mechanisms not yet sufficiently investigated. Thus, muscle spindle activity is regulated at the spinal level by the gamma motoneuron system which in turn is regulated by supraspinal extrapyramidal structures, including the reticular formation, the niger and the pallidum.

Continuous integration of peripheral and central impulses in different structures occurs in this motor regulating system according to Hess' conceptions of proprioceptive steering, von Holst's principles of *Reafferenz* (280) and other cybernetic rules. Several servomechanisms with positive and negative feedback are probably active at different levels, cerebral and spinal. At the lower levels they work according to von Holst's reafferent principle, the gamma system serving as an additional amplifying protective mechanism. At higher levels the vestibular regula-

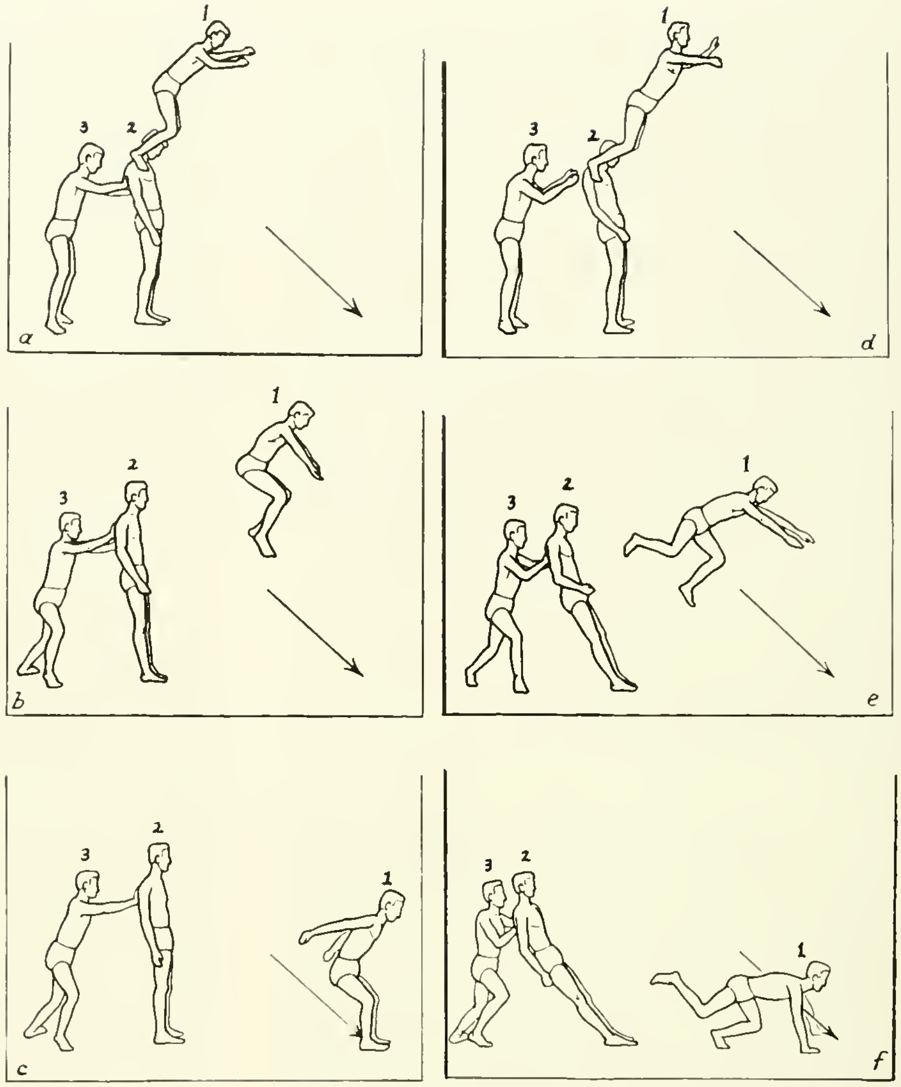

FIG. 13. Model of teleocinetic and ereismatic motility. Three persons represent the actions and reactions involved in an intentional motor performance. The 'teleocinetic' leaper (*1*) is supported by the 'ereismatic' carrier (*2*) and supporter (*3*). *a* to *c*: The leap succeeds when the right support is given and when the carrier knows the moment at which *1* jumps. *d* to *f*: The same leap without supporting activity fails. The unsupported and unprepared carrier falls backward and is only caught by emergency action of *3*. The leaper jumps too short and also falls because of lack of the proper support. (Redrawn from an unpublished motion picture made by Hess in 1943.)

tions are recruited when the lower mechanisms become insufficient and falling is imminent. The precise mechanisms of these extrapyramidal postural regulations and their relation to teleokinetic motor activity need more experimental study.

Some essential differences between the head and eye movements of man and those of quadruped mammals are important for the understanding of extrapyramidal direction-specific responses. *a*) In man, eye movements are more prominent and used more frequently than in animals mainly moving the head. Cat optomotor reactions concern the head more than the eyes. *b*) The various planes of movement and the spatial relations of the eyes, head and trunk are different in man and quadrupeds. The upright position of man and the position of his head and eyes relative to his trunk requires a totally different motor organization. Therefore it is not permissible to homologize Hess' findings in the cat with the conditions in man [Jung (132)] since the eye movements of these two species are similar only relative to the head. In man, a turning movement in the horizontal plane is effected by rotation of the head and eyes relative to the trunk and would correspond in the cat to a similar rotatory movement effected in the vertical plane. Conversely, the turning movements of cats in the horizontal plane would correspond to rotatory movements of the head in man. Intentional turning of the body in man shows the succession of eyes, head and body while passive turning movements produced by vestibular stimuli have an opposite succession of body, head and eyes [Güttich (73), Jung (134)]. In active

movements, which are primarily teleokinetic, the eyes are leading, sensory anticipation and safeguarding mechanisms being the motor accompaniments of the shifting attention. By contrast, vestibular correction movements are mainly ereismatic mechanisms to maintain normal posture.

What we have called physiological anticipation of motor action, including its attentional and sensory component, is probably similar to what Auersperg (8) called 'prolepsis,' coined for the regulation of eye movements. It seems evident that these functions of motor readiness, anticipation of action and attention should work in close connection with the nonspecific activation system of the brain stem. However, from observations of apraxia after cortical lesions in man showing defects of this anticipatory action it seems probable that the human cerebral cortex and thalamocortical connections play a prominent part in motor anticipation. The extrapyramidal centers, the reticular formation and the spinal gamma system seem to be the effector mechanisms of this function.

UPRIGHT POSTURE IN MAN AND ITS ONTOGENETIC DEVELOPMENT. The upright posture, which is peculiar to the human species, is intimately related to nearly all of the characteristic human aspects of motility: the freedom and specialization of the hands, the different position of the head, and the prominence of eye movements [Straus (249)]. It seems logical to assume that the extrapyramidal motor system in man must be organized differently from that of other animals to provide the neural substrate for the upright posture and walking. Further, the erect posture requires a more elaborate regulatory process to oppose gravity and to protect against falling. These mechanisms are active only in the waking state and require continuous support by the thalamoreticular activating system.

Erect posture and locomotion are acquired by the infant during the first 2 years of life. Only in the second half of the first year does sitting and standing become possible. Locomotion comes later, developing from crawling to walking around the 12th month. These functions evidently require the regulating mechanisms from various proprioceptors and a well developed extrapyramidal system, coordinated with cerebellar and pyramidal structures and partly modified by learning.

A detailed comparison of Magnus', de Kleyn's and Rademaker's findings in animals with the motor behavior of normal infants at different ages is given in Peiper's book (207). The development of erect posture and the different locomotor activities that precede it were studied by Schaltenbrand (223) and Peiper (207). When a human infant begins to raise the body from the supine position by a characteristic turning movement, the eyes and the head lead in a manner similar to the rotatory movements of animals elicited by mesodiencephalic stimulation. During the 2nd and 3rd year of life these body raising coordinations are altered to a rotation of the pelvis and in the 4th and 5th year rotation is replaced by a supporting action of the arms so that the trunk is brought directly to a sitting position [Schaltenbrand (223)].

Adversive turning movements of eyes, head and foretrunk, instinctive orientation movements induced from various receptors and central regions, are normally integrated into a versatile motor behavior. They appear as isolated mechanisms in infants and may be released after diffuse cerebral lesions. In patients with senile dementia they may be interpreted as syndromes of organic regression to infantile mechanisms.

MOTOR PERFORMANCES OF HUMAN ANENCEPHALI. The behavior of infants without cerebral cortex and with various degrees of preservation of the basal ganglia and brain-stem nuclei is of special interest for extrapyramidal functions. It seems safe to conclude that the motor patterns and instinctive reactions observed in anencephalic brain-stem creatures are mediated by lower brain-stem structures.

In the normal human newborn the cortex, the striatum and their pathways are nearly unmyelinated, but the pallidum and the subthalamic nucleus are well myelinated and probably can function normally except for their connections with the cortex. The pallidum is the highest motor center in newborn human infants during the first weeks of life. Therefore, they have been called *Pallidumwesen* or *Thalamuspallidumwesen* by Foerster (57) and have been compared with pallidothalamic animals by some authors. Their motor and instinctive reactions are probably coordinated mainly by subcortical mechanisms.

The most extensively studied human anencephalus living some months without cortex and upper basal ganglia and examined anatomically later in detail is Gamper's *Mittelhirnwesen* (66, 67). The brain of this creature contained an intact mesencephalon, pons, oblongata and cerebellum, but no cortex, striatum or pallidum; only a few traces of the diencephalon were present. Some of its instinctive actions are described in the subsequent section on attention patterns. Although it showed tonic neck and labyrin-

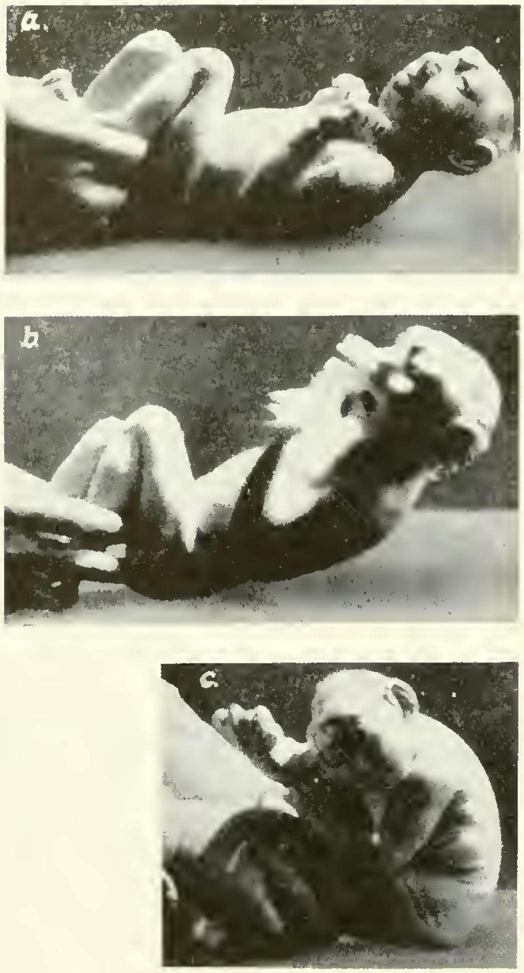

FIG. 14. Reflex sitting up in mesencephalic child. After pressure on the legs, the anencephalus without cortex and basal ganglia rises to a sitting position. Only the extrapyramidal structures below the diencephalon were preserved; the red nucleus, cerebellum and central tegmental tract were intact. [From Gamper (66).]

thine reflexes, the righting reflexes were also preserved and Moro's reflex was intact. This creature resembled mesencephalic animals according to Magnus' own opinion.

Gamper's child had no decerebrate rigidity in contrast to the children without cortex described by Edinger & Fischer (53) and by Jakob (129) in whom the pallidum remained intact and who showed a marked rigidity and akinesis resembling decerebrate animals. Gamper's child had reduced motor performance but would assume a sitting position when both lower legs were pressed (fig. 14). This child, using only his midbrain, pons and cerebellum, was far better off in motor performance than other anencephalic children having more of the basal ganglia preserved and reaching a greater age. This contrast arises because the pallidum is the main structure for inducing rigidity in Parkinsonism. In all these anencephalics there was atrophy of the substantia nigra. Those with the pallidum intact showed rigidity preventing normal postural reactions, but Gamper's child had no pallidum and therefore less rigidity.

Another 'mesorhombencephalospinal' anencephalus having neither basal ganglia nor cerebellum was studied by Monnier & Willi (194, 195) to the age of 2 months and was compared with a rhombencephalic bulbospinal anencephalus. As one might expect from the lack of cerebellum and red nucleus, it showed less motor ability than Gamper's case but more than the rhombencephalic one. Some mimic expressions of aversion after pain and well-being after satiation and warmth were preserved in the mesencephalic case. This creature generally assumed a sleeping attitude without spontaneous alteration of sleep and wakefulness, but showed arousal after sensory stimulation. Four pontobulbar anencephali ('rhombencephalic beings') observed by Monnier & Willi (193–195) lived only 1 to 3 days. All had disturbances of respiration which was irregular, snapping or periodic. Spontaneous motility was absent but reflex movements could be elicited: spinal reflexes, Moro's reflex and grasping reflexes were present. Oral feeding activity could be evoked by tactile stimulation of the mouth and cheeks. The sucking reflex was well developed in only one of these cases. Tonic neck reflexes were absent, the righting reflexes doubtful. There was no decerebrate extensor rigidity but increased flexor tone of the limbs appeared in all four cases. Histological studies of the brain showed the pontine structures partly developed in one, but only bulbar structures in the other three cases.

DECEREBRATION PHENOMENA. The mechanism of decerebrate rigidity primarily involves the lower brain-stem centers and therefore does not concern us here. But it is to be remembered that the main condition for exhibition of decerebration phenomena is an elimination of the higher regulation of posture by diencephalic and midbrain structures (including the *Stellreflexe* of Magnus, Rademaker and co-workers, and the *Richtungsbestimmte Bewegungseffekte* of Hess). Rademaker's claim of a prominent role of the red nucleus for *Stellreflexe* and the appearance of decerebrate rigidity after red nucleus destruction was not confirmed by Mussen and others, using more selec-

tive lesions. However, tegmental mesencephalic lesions are still among the main condition for decerebration. The motor functions of the midbrain structures have appeared in a new light since recent studies of the supraspinal control of the gamma motoneuron system. We must distinguish between two types of decerebrate rigidity reacting differently to posterior root section and to chlorpromazine. *a*) The classical Sherrington decerebration following intercollicular transection shows a very marked hyperactivity of gamma efferents which can be diminished by chlorpromazine [Henatsch & Ingvar (95)]. *b*) The decerebration rigidity following lesions of the anterior cerebellum or produced by the anemic method of Pollock and Davis shows no hyperactivity of the gamma system but rather direct activation of the alpha motoneurons [Granit (69)] and is less sensitive to dorsal root section and chlorpromazine. An anatomical correlation of these two types with different brain-stem structures and their functions cannot yet be made. Granit & Holmgren (70) have postulated two different pathways for activating gamma neurons, one a slow and polysynaptic mechanism through several spinal segments, the other a fast mechanism mediated through the lateral columns probably by reticulospinal fibers.

Startle Reaction

The startle reaction after unexpected sensory stimuli (usually acoustic) seems to be mainly an extrapyramidal motor response. It has been studied extensively by Strauss (250) who distinguished between primary and secondary startle reactions by kinematographic analysis of the phenomena (*Zusammenschrecken*) following a pistol shot. Strauss believes the primary reaction to be an acousticomotor reflex in the lower brain stem, involving the red nucleus. The secondary reactions are partly emotional or voluntary movements and may involve the cerebral cortex and are less constant. Increase in the primary reaction was found in spastic limbs and in some akinetic patients without rigidity. Diminished primary reactions were found in parkinsonian syndromes showing rigidity and tremor and in chorea and athetosis. Startle reactions may be absent during sleep. As startle reactions and Moro's reflex are also observed in human anencephali, it seems highly probable that they are mediated by the lower extrapyramidal centers with the reticular formation.

Electromyographic studies of the startle reactions by Duensing (46) distinguished a short latency startle (*Schreckreflex*) and a long latency startle (*Schreckreaktion*), involving different muscles. Duensing believed that both startle reactions use the same efferent bulbomesencephalic and spinal pathways, but that the long latency reactions also involve the thalamus or the striatum.

Tremor

Phylogenetic parallels between extrapyramidal movements and motor performances of animals have been discussed since Foerster (57) compared athetosis with the climbing movements of monkeys. The similarities of tremor with the fin movements of some fishes (fig. 15) were believed by Jung (130) to indicate the existence of coordinating mechanisms in the spinal cord similar to those described in spinal fishes by von Holst (278). Therefore, tremor was interpreted as an archaic simple form of rhythmic antagonistic movements, released by disturbances of higher mechanisms. The physiological tremor of shivering investigated electromyographically was found similar in man [Denny-Brown *et al.* (43)] and animals [Burton & Bronk (28)]. The latter found, as did Jung (130), that most motor units discharge only once in one tremor beat.

Parkinsonian tremor, the rhythm of which may be different in different limbs, shows little dependence upon afferent control and seems to be mainly an autogenous rhythm arising in the interneuronal system of the central nervous system [Jung (130)]. Central tremor rhythms independent of reflex control were first postulated by Wachholder & Altenburger (282). Altenburger (6) showed that tremor persisted in deafferented limbs after posterior root section, although Strughold (250a) and Hoffmann (119) had found some slowing of clonus rhythms after loading the muscles and therefore considered proprioceptive modification possible. This was recently confirmed in tremor by Halliday & Redfearn (76). These observations, however, seem not to be conclusive for the 'servoloop' theory of tremor [Halliday & Redfearn (75)] and do not prove their contention that integrity of the reflex arc is essential for tremor rhythms. Proprioceptive tendon reflexes elicited during parkinsonian tremor show a rhythmic facilitation or inhibition depending upon the alternating reciprocal innervation of the reflexly excited muscles [Jung (130)]. In contrast to many older theories considering cortical and subcortical mechanisms to be the source of tremor rhythms, Jung (130) localized the central substrate of tremor in the interneuronal

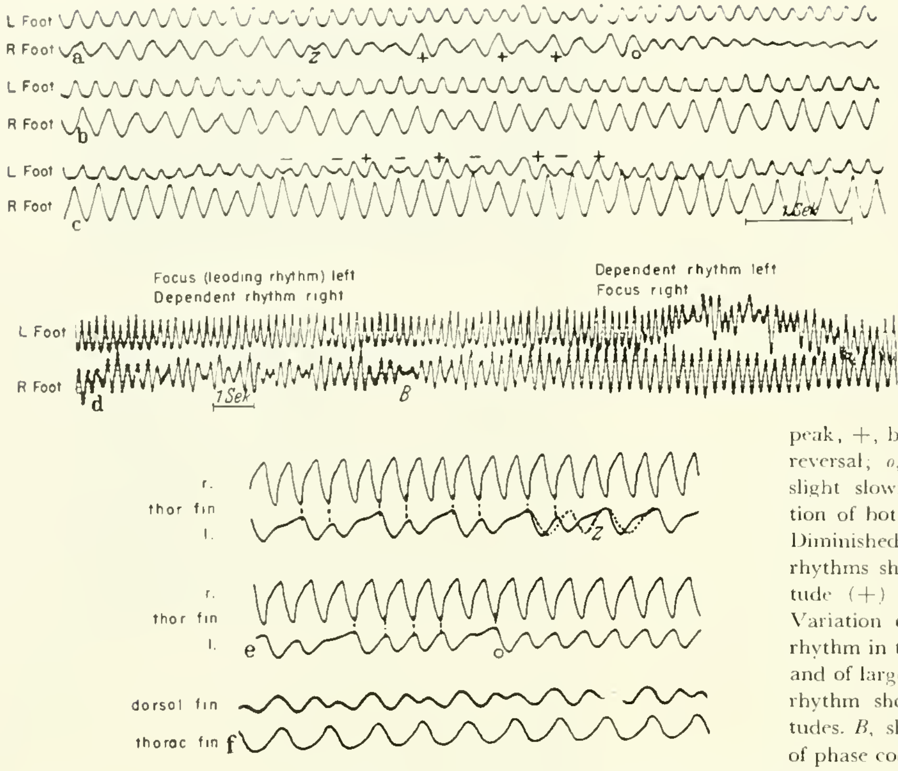

FIG. 15. Bilateral parkinsonian tremor in man (*a* to *d*) and fin movements of fishes (*e* and *f*) illustrating the 'relative coordination' of von Holst. The rhythmic movements of the two sides are independent at the start of each record and later show different coordination phenomena varying in short time intervals. *a*: Phase coordination (von Holst's 'magnet effect') with a tendency to phase reversal and alternating movements of the two sides. *Z*, an intermediate beat (*Zwischenschlag*) with double peak, +, beats with larger amplitude and phase reversal; *o*, absolute phase coordination with slight slowing of right foot. *b*: Independent action of both rhythms. *c*: Central superposition. Diminished amplitude of left foot (−) when both rhythms show phase reversal, and larger amplitude (+) when they are beating in phase. *d*: Variation of dominant focus. The dominant rhythm in the region of the focus is more regular and of larger amplitude. The other (dependent) rhythm shows irregularities and lower amplitudes. *B*, short blocking of rhythm. *e*: Periodicity of phase coordination in fin movement. *Z*, intermediate beat and its development from the original rhythm ( ) by attraction of reversed phases (¦); *o*, absolute phase coordination similar to human tremor in *a*. *f*: Amplitude variations of dorsal fin movements similar to human tremor in *c*. [From Jung (130, 133).]

bulbospinal system. As all bulbospinal interneuronal systems receive proprioceptive input, it did not seem surprising that some reflex mechanisms would also interfere with tremor. But, as Walshe (289) had shown in 1924, tremor rhythms are usually independent of reflex mechanisms and proprioceptive influx, whereas rigidity disappears after novocainization of muscles. The mechanism of this procaine effect, however, cannot be a pure blocking of proprioceptive influx as Liljestrand & Magnus (162) assumed since cocainization inactivates efferent gamma fibers before the large fibers of proprioceptive afferents are affected [Leksell (158), Matthews & Rushworth (178)]. The effects of stereotaxic operations in man show a diminution of tremor following thalamic and pallidal lesions. Therefore, a facilitative influence of these cerebral structures upon the lower mechanisms of tremor movements has to be assumed (see also p. 885).

Hyperkinesis in General

A general explanation of extrapyramidal hyperkineses can be drawn from Hess' conceptions (106–108) of a physiological balance of several direction-specific 'forces' in motor and postural regulation: if the regulation of movements results from a delicate balance of several forces, oriented in the three dimensions of space, a lesion in one of these regulation centers should induce oppositely directed movements. The muscular contractions in these movements may be either tonic as in torsion dystonia, torticollis and partly in athetosis, or intermittent as in chorea and hemiballism. There is a remarkable parallel between the tonic deviations of Hess' cats and certain extrapyramidal syndromes in man in that both are apparent only in the waking state with active postural background innervation and that they are induced or increased by active movements and emotional tension. Generally the movements should be the mirror image or opposite of the stimulation effects caused by a release of the forces of innervation normally balanced by the damaged center. This is indeed the case in midbrain lesions as shown in figure 10. Such an explanation was first used by Monnier (192) for torticollis as a result of Hess' findings. It is in agreement with Jackson's classical explanation of positive

neurological symptoms as a release of mechanisms from the inhibitory action of higher centers. This principle of release also can be used for disturbances of coordination at one level or even within one structure. Denny-Brown (40) has used it to explain involuntary movements caused by disorders of integration between the rolandic and extrarolandic cortical areas.

Independently of Hess' concepts, Denny-Brown has extended this principle to lower levels. He considers athetosis and dystonia as "conflicting extremes in the pattern of control of the basic organization of the tegmental mechanisms by rolandic and extrarolandic cortex," a "disequilibrium due to loss of one member of a balanced pair rather than as a release of a function by loss of an inhibitory suppression of this function." Such a disturbance may provide an explanation of many of the strange symptoms of extrapyramidal diseases.

Parkinsonism provides a good example of the fallacies arising from attempts to explain signs exclusively in terms of the Jacksonian distinction between positive signs, arising by release of inhibition, and negative signs caused by loss of function of the affected region. In parkinsonism the loss of associated movements in walking attributed to destruction of the substantia nigra is certainly a negative sign. However, these movements return if the pallidum is also destroyed. Thus these movements cannot be interpreted as being mediated solely by the substantia nigra.

It is not yet clear whether in *épilepsie giratoire* some of the rotatory movements and adversive convulsions are mediated by the mechanisms of the brain stem and whether they are elicited by subcortical release or by active stimulation from a cortical epileptic focus, such as the frontal or occipital areas for head and eye deviation.

Extrapyramidal System and Spinal Reflex Activity.

As clinical observations had shown that extrapyramidal diseases of the basal ganglia have less influence on reflex activity than do pyramidal lesions, one might not expect much information from animal experiments in this field. Therefore, only a very few such investigations have been made.

Lloyd's (165) studies on reticulospinal pathways included an important electrophysiological analysis demonstrating the connection of the bulbar extrapyramidal structures with the motoneurons and interneurons of the spinal cord, resulting in synchronization of internuncial activity. The functional organization of this system is such that secondary vestibular fibers through the dorsal longitudinal bundle and vestibulospinal tract, together with reticulospinal fibers, constitute the main extrapyramidal input which is correlated with corticospinal impulses at all levels. This system contains not only short fiber relays but also long fiber connections of the reticulospinal and propriospinal tracts with rapid conduction rates. Facilitation of two-neuron reflexes after electrical stimulation of the descending bulbospinal tracts was described.

Peacock & Hodes' (206) experiments on the modification of the cortical stimulation effects by stimulation of the basal ganglia, described in the section on the striatum, included the finding that monosynaptic spinal reflexes were inhibited by caudate stimulation. In contrast, unpublished experiments of Segundo and co-workers on cats have shown that ventral root discharges in the L7 segment evoked by dorsal root stimulation are usually augmented but occasionally reduced by repetitive stimulation of higher extrapyramidal centers (the caudatum and putamen as well as the pallidum and claustrum). Diminution of reflex response was obtained only from the striatum (caudatum and putamen). Since dorsal root stimulation elicits many reflex mechanisms synchronously which are never activated at the same time under physiological conditions, such studies do not allow differentiation of reflex activity except as to monosynaptic and polysynaptic reflexes. Therefore, the functional interpretation of their results is very limited. It may be concluded, however, that the striatum appears to exert a regulatory effect on motor reflex mechanisms which includes both excitatory and inhibitory components.

The recent discovery of the spinal gamma fiber system for regulation of muscle spindle activity and its dependence on a brain-stem mechanism has aroused much interest since this system now appears to be involved in production of certain extrapyramidal motor disorders.

The basic physiological findings concerning this system are described in Chapter XLI in this *Handbook* by Eldred on posture and locomotion. Much of the evidence that the activity of this system is altered in extrapyramidal diseases has already been presented in this chapter and need only be summarized here. First, the rigidity of parkinsonism depends in considerable degree on abnormal gamma system participation in reflex control of muscle length and tension. Second, in observations on reflex reinforcement in man, Hassler (88) and others showed that

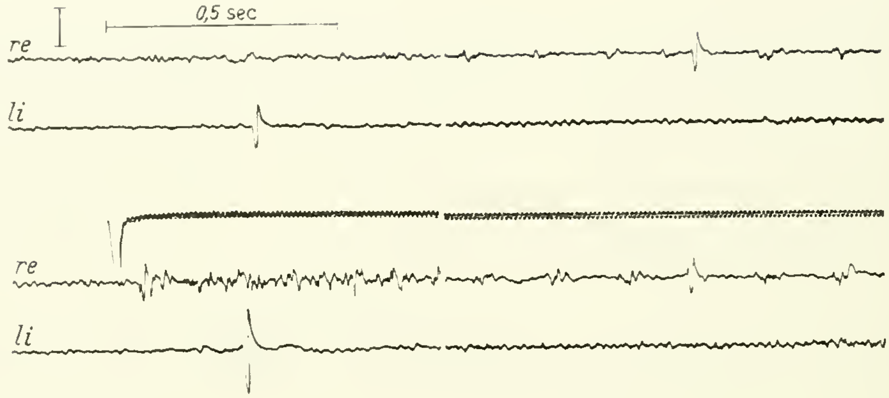

FIG. 16. Deficiency of reflex facilitation by gamma activation in an unilateral parkinsonian syndrome. Electromyograms of right (*re*) and left (*li*) biceps brachii in a patient with right-sided parkinsonism. *Upper records* show monosynaptic tendon reflexes elicited by striking the forearm. *Lower records* show the same responses after clenching the contralateral fist, a procedure which produces reflex facilitation of muscle spindles in man (118, 236). Marked potentiation of reflex appears on the normal left side, but no potentiation on the affected right side. Some rhythmic tremor potentials appear in the background of the right biceps EMG. [From Hassler (88).]

the Jendrassik procedure for facilitating tendon reflexes is less effective in Parkinson's disease (fig. 16). It has been known since Sommer's (236) experiments that this procedure works by facilitation of muscle spindle activity. Since Leksell (159), Granit and coworkers (71) and Hunt & Kuffler (120, 121) have shown that muscle spindle activity and reflex reinforcement are regulated by the gamma motoneurons, one may conclude that activation of this system is defective in parkinsonian patients having lesions in the substantia nigra.

Apparently two different reflex control mechanisms, postulated by von Holst (280) in his principle of *Reafferenz*, regulate muscle length and muscle tension by negative feedback: *a)* for muscle length, involving the annulospiral endings, modified by gamma innervation and eliciting monosynaptic reflexes, and *b)* for muscle tension, with the flower-spray endings activating interneurons. Inhibiting impulses relaxing muscle tension originate in the tendon organs. Two kinds of alpha motoneurons exist with predominantly either phasic or tonic function. The tonic neurons show a more prolonged after-hyperpolarization, and lower conduction velocities and discharge frequencies than do the phasic neurons [Eccles (50, 51)]. In parkinsonian rigidity the quick adaptation mechanism of the gamma system is defective and the tonic alpha system is overactive although the reflex mechanisms of the phasic alpha system (the monosynaptic reflexes) seem to be normal.

A special kind of pathological exteroceptive intersegmental reflexes was described by Duensing & Schneider (49) in human athetosis and further studied by Duensing (44, 45) as *pathologische Fremdreflexe*. These reflexes were not observed in other extrapyramidal syndromes except in some cases of myoclonus, hemiballism and acute encephalitis. In the electromyogram Duensing's reflexes show a biphasic form of synchronous motoneuron discharge similar to that of the monosynaptic reflexes, but their latency is two to three times longer than that of corresponding proprioceptive reflexes. The response in these reflexes consists of single muscle twitches which are evoked by striking, scratching or tapping wide and often distant cutaneous areas. Duensing (45) believes that these reflexes are release phenomena resulting from facilitation in spinal interneurons controlled by brainstem structures, probably the reticular formation.

Relation of Extrapyramidal Mechanisms to Thalamoreticular System: Sleep and Arousal, Motor Patterns of Attention

Clinical observations on extrapyramidal disorders in man have long shown their dependence upon the waking state. Every type of extrapyramidal hyperkinesis (tremor, chorea, athetosis and ballism) disappears during sleep and reappears with arousal. Although the profound muscular atonia of sleep influences all motor mechanisms including even spinal reflexes, the relation of extrapyramidal mechanisms to

arousal and sleep seems to be particularly evident. However, similar evidence in animals came rather late. Anatomical connections of the extrapyramidal nuclei with the medial thalamus and the reticular formation were known long ago, but their functional significance became evident only when the general importance of the nonspecific thalamoreticular system was recognized after the pioneer work of Hess, of Morison & Dempsey and of Magoun & Moruzzi

A sleeplike syndrome can be induced by caudate stimulation and pallidal destruction. Early experiments of Hess had shown that stimulation not only of the medial thalamus but also of the caudate caused sleep or sleeplike behavior in cats. Later observations of Akert and co-workers (3, 4, 5) in Hess' laboratory have shown that weak repeated stimulation of the caudate by low frequencies causes diminution of motor readiness in cats that can be distinguished from sleep (*striäres Inaktivierungssyndrom*) (fig. 5, right side). Heath & Hodes (94) have induced sleep by caudate stimulation in monkeys and man.

Hess has interpreted his and Akert's stimulation experiments on the caudate as an inhibition of motor mechanisms irradiating to the whole sensorimotor system because proprioceptive correction of posture is also affected, mainly on the contralateral limbs. Hess (107) believes that the caudate nucleus plays a part in the regulation of somatomotor readiness. In contrast to the general diminution of activity and of readiness caused by stimulation of the hypnogenic zone in the medial thalamus, exteroceptive and vegetative mechanisms seem to be less affected by caudate stimulation. In Hess' opinion stimulation of the caudate elicits only a part of the integrated mechanism for sleep causing a state similar to the *Partialschlaf* observed in man, particularly in some neurological disturbances of sleep and muscular tone (narcolepsy and cataplexy).

Electrophysiological observations of brain potentials with implanted electrodes corroborate these findings. Subcortical leads in patients [Knott *et al.* (151), Meyers *et al.* (189)] and in monkeys [Hodes *et al.* (116)] have demonstrated that the earliest electrical changes in drowsiness appear in the caudate nucleus. This was true for both natural and barbiturate-induced sleep. Electrical activity characteristic of sleep (bursts of 1 to 3 per sec. high voltage waves with occasional 8 to 10 per sec. waves and later 15 to 20 per sec. spindles) occurred earlier in the subcortical structures than in the cortex. Hodes and co-workers discuss the possibility of subcortical driving of the cortex, but they are cautious enough not to locate the primary action in any particular nucleus. However, the induction of sleep by stimulation of the caudate by Heath & Hodes and sleeplike behavior by Hess, Akert and co-workers seem to indicate that the caudate is an important center for inactivation of the cortex. The results of electrical stimulation of the caudate in cats, monkeys and men and their bioelectrical effects have been discussed previously in the section on the striatum.

The effects of pallidotomy in human extrapyramidal hyperkinesis also indicate a role for the pallidum in sleep regulation, since a constant result following immediately after its extensive destruction is drowsiness often progressing to real sleep. (See also the earlier section in this chapter on the pallidum.)

Further indications of the close coordination between extrapyramidal motor functions and the nonspecific reticular system may be seen in the inhibition of vestibular nystagmus during sleep noted by Keser (148) and Jung (134), and the parallel between the

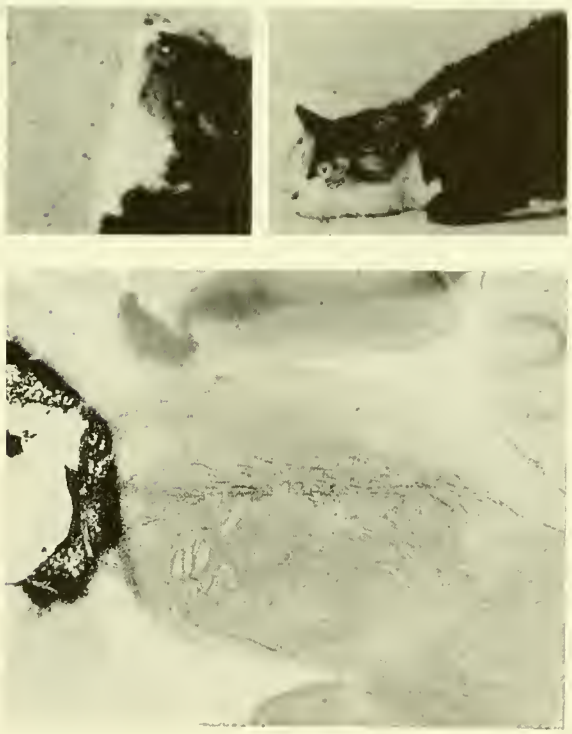

FIG. 17. Adynamia after a large coagulation lesion of the posterior hypothalamus. *Upper left:* Electrical stimulation before coagulation causes raising of head and pupil dilatation. *Upper right:* After coagulation head and foretrunk are lowered, and muscle tone weakened in the legs. *Lower:* Coagulation destroys the dynamogenic zone of posterior hypothalamus and the praestitial nucleus. (From Hassler, in Hess' unpublished collection.)

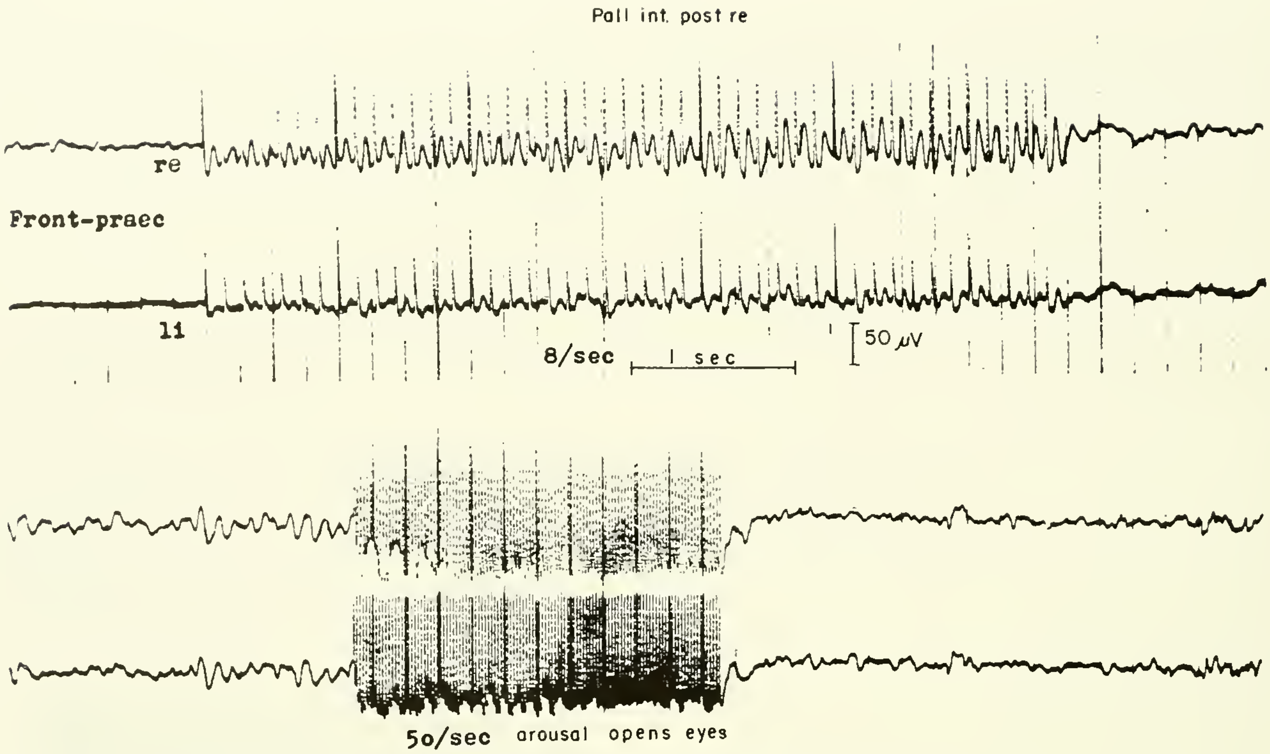

FIG. 18. Nonspecific effects of pallidum stimulation on the human EEG. Recruiting potentials at 8 per sec. and desynchronization with arousal at 50 per sec. stimuli. During stereotaxic operation on a parkinsonian patient the right internal posterior pallidum was stimulated by thyratron impulses preceding coagulation. *Upper record:* 8 per sec. stimulation (12 v. peak strength) elicits recruiting waves mainly in the homolateral right (*re*) frontoprecentral region with increasing amplitude and some waxing and waning, less effect in the contralateral (*li*) region. *Lower record:* 50 per sec. stimulation (4 v.) through the same leads causes acceleration of rhythms and some flattening following the stimulus series. Some alpha waves continue in the first 300 msec. of stimulation. Arousal with opening of the eyes appeared during stimulation. [From Umbach, unpublished observations.]

arousal type of EEG and gamma activity causing muscle spindle discharge found by von Euler & Soderberg (276).

At higher diencephalic levels of the thalamoreticular system coordination with extrapyramidal structures becomes very close. Hess described as *Adynamie* a syndrome showing loss of muscle tone and spontaneous activity occurring after coagulation of the posterior hypothalamus (see fig. 17). He called this region bordering the oral part of the mesencephalic reticular formation the 'dynamogenic' zone. *Adynamie* seems to be a milder variant of the syndrome that Magoun and his school found after coagulation of the anterior mesencephalic mid-line region in cats and monkeys which resulted in a coma simulating sleep with marked slowing of EEG rhythms [Lindsley & co-workers (163, 164)].

Among the direction-specific effects of mesodiencephalic stimulation described by Hess, the body raising responses evoked from the lower mesodiencephalic structures, the prestitial and red nuclei (figs. 8, 17) have special importance for the waking attitude and the posture of attention.

The motor patterns of attention are regulated by the extrapyramidal mechanisms in close association with the tegmental motor system. This system, the nucleus motorius tegmenti (*motorischer Haubenkern*) of Edinger (52), includes, besides the efferent motor nuclei of III, IV, V, VI, VII, and IX to XII cranial nerves, the red nucleus and the nucleus vestibularis of Deiters, and also the reticular formation. A number of rhythmic motor phenomena, such as nystagmus and respiration, are regulated by this system. Among these are the opening of the eyes or adversive move-

ments of the eyes and head, together with alterations of muscle tone and of mimetic innervation related to attentive arousal. These nonspecific effects are observed after stimulation of many structures from the cortex and basal ganglia to the brain-stem reticular formation. The many structures involved in the ipsi- and contraversive turning effects are summarized in figure 11. Apart from the above mentioned body-raising responses, we cannot assign special components of these motor patterns of attention to special nuclei of the extrapyramidal system. However, one of the more important reticular functions is the regulation of eye movements and nystagmus which are among the motor correlates of attentive behavior. Vestibular as well as optokinetic nystagmus is coordinated in the pontine and mesencephalic reticular formation. Recent unit analysis in the medial lower reticular formation by Duensing & Schafer (47, 48) has disclosed two groups of neurons, the first having fixed relations to certain phases of nystagmus and showing reciprocal action in the slow and rapid phases of nystagmus, the second being loosely coupled with nystagmus and primarily activated by general arousal.

Stimulation experiments during stereotaxic operations have shown that the motor accompaniments of general arousal can also be obtained from various structures in man. They have been observed after stimulation of the centromedian thalamus (fig. 7) and other intralaminar nuclei [Hassler (85, 86), Jung (135)], as well as from the pallidum, accompanied in the latter case by an arousal type of EEG as shown in figure 18. Although weak low-frequency caudate stimulation may cause inactivation, stronger stimuli or higher frequencies elicit unilaterally directed attention to the contralateral side as a part of motor readiness. Lower brain-stem structures have not yet been investigated in man.

Arousal, however, can be observed after stimulation of various structures outside the nonspecific activation system, especially when tetanic stimuli at high frequency are used, for example that reported by Buchwald & Ervin (19) after such stimulation of the caudate and pallidum and of the amygdala and other rhinencephalic structures, as well as that obtained by French *et al.* (62) from several regions of the cerebral cortex.

Periodic alternation of sleep and wakefulness was present in Gamper's mesencephalic anencephalus although no cerebral cortex and practically no diencephalic structures were preserved. Thus, even in man the mesencephalic and pontine parts of the nonspecific activation system alone may be able to induce changes similar to sleep and wakefulness behavior in the intact organism.

Finally, a few general remarks on the reticular formation should be made. This structure seems to be the main lower center for extrapyramidal motor functions, and especially for bilateral coordination. Bilateral functions are insufficiently brought together in the higher diencephalic and telencephalic centers, there being no commissures and only a few fibers connecting the symmetrical nuclei. In contrast to this the mesencephalic and rhombencephalic reticular nuclei have an abundance of crossing fibers. The neurons of the reticular formation seem also to be specifically suited for longitudinal coordination between caudal and oral centers because their large axons have very many collaterals; one reticular cell may have a ramifying axon reaching from the upper cervical cord caudally to the nonspecific thalamic nuclei cranially, as the Scheibels (225) have shown.

Caudate and pallidum stimulation produces widespread bilateral evoked potentials in the cerebral cortex similar to the recruiting waves obtained from the nonspecific thalamic nuclei and reticular formation [Ajmone-Marsan & Dilworth (2), Shimamoto & Verzeano (233), Umbach (260), and Hassler (85)]. This is a further argument for the close relation of the higher extrapyramidal centers to the nonspecific activation system of the brain. Similarly, previous conditioning stimulation of the mesencephalic reticular formation facilitated and amplified the effects on the cerebral cortex and other telencephalic structures of test stimuli applied to the caudate [Umbach (262)].

One sometimes tends to forget, during the present vogue of brain mythology about consciousness and attention, that the reticular formation is mainly a motor coordinating center, the lower part for respiration, the higher parts for eye movements and body posture. The psychological effects of attention and conscious acts are only secondary specializations, derived from basic reticular functions controlling motor behavior, and preponderant solely from an introspective and anthropocentric viewpoint.

Relation of Extrapyramidal Functions to Instinctive Behavior

As mentioned above, all motor mechanisms of the lower mammals and other vertebrates are 'extrapyramidal' by definition because these animals have no pyramidal tract. A full treatment of the results of behavioral research on animals cannot be given here, but certain general trends should be mentioned

which have yielded some clues for the understanding of the extrapyramidal system. It is certainly no accident that the favorite animals for behavior studies are birds which have a highly developed striatum but a negligible cortex. Not only the original observations on instincts by Whitman, Craig and Heinroth but also all important discoveries made recently in this field, such as motivation activities and innate releasing mechanisms or *angeborenes Schema* of Lorenz, imprinting or *Prägung* of Lorenz (168–170), and the displacement activity or *Übersprung* of Kortlandt (153) and Tinbergen (253), were first described in birds in which the striatum is the main forebrain structure.

The study of innate behavior now called 'ethology' is best described in Tinbergen's book (253). Some correlations with neurophysiological findings have been proposed by Prechtl (212, 213). However, the coordination between ethology and neurophysiology is still in its earliest stages.

EXPERIMENTS ON BASAL GANGLIA OF BIRDS. The first worker to take advantage of the unique opportunities for study of basal ganglia function afforded by birds was Kalischer (140, 141). Using parrots because of their complex foot movements and capacity for speech, he carried out stimulation and extirpation experiments on the relation of the cortex and striatum to instinctive behavior. He found that in these birds the mesostriatum is the main sensorimotor coordination center, especially for feeding mechanisms. Bilateral incomplete lesions of the mesostriatum caused severe disturbances of speech and feeding mechanisms whereas unilateral lesions resulted in slight disturbances. Lesions of the hyperstriatum (which in his opinion is equivalent to the caudate nucleus in mammals) resulted in defects of contralateral turning movements. The motor coordination of these movements was believed to be dependent on the mesostriatum. Kalischer believed the hyperstriatum to be a higher center of sensorimotor functions for 'orientation,' the sensory influences coming mainly from the mesostriatum and epistriatum. Lesions in the ectostriatum may cause disorders similar to those in the hyperstriatum. The epistriatum has relations to visual functions since it is the highest optic center superimposed on the mesencephalic (tectal) visual structures. The higher coordination of vision, especially of foveal function in birds, is not a function of the cortex but of the striatum. The negligible parts of cerebral cortex present in parrots do not have much importance for motility and speech and can be extirpated without serious impairment of these functions. The birds' forebrain mechanisms are mainly coordinated by the striatum, with the exception of the rhinencephalic functions.

In Roger's (219) important early brain-stem studies in pigeons, the effects of ablation of cortex and striatum on instinctive behavior were observed. He concluded that the ectostriatum and mesostriatum were essential to the behavior of feeding, drinking, fighting and courting and that more complex instinctive actions as mating, nesting, incubation and rearing the young require the hyperstriatum. Loss of the cerebral cortex with the hyperstriatum intact was followed by no characteristic behavior deficiencies. These decorticated birds fed and protected themselves normally. When cortex and hyperstriatum were eliminated the birds, after a period of helplessness, again became able to feed themselves but never regained mating and nesting behavior. Rogers concluded that simple association or learning processes in correlation with behavior cycles can be carried out without cortex by lower brain structures, including the hyperstriatum and possibly also the hypopallial area. Rogers believed that the epistriatum is a visual coordinating center and the ecto- and mesostriatum are primary centers for spontaneous feeding, confirming Edinger's view that the basal parts of the corpus striatum are essential for feeding reflexes.

In recent experiments on the chicken brain, von Holst (unpublished observations) studied the effects of simultaneous stimulation with implanted electrodes at two separate points in the brain stem which activate different types of instinctive behavior. He found that some of these overlap and occur simultaneously whereas others were mutually exclusive (for example, feeding and nesting behavior), in that when stimulation evoked one drive, the other was suppressed. When two loci in the brain producing exclusive drives were simultaneously stimulated, the suppressed behavior reappeared explosively as a rebound after stimulation was stopped.

INSTINCTIVE BEHAVIOR AND BASAL GANGLIA IN FISHES. In fishes (sticklebacks), all special instinctive actions are preserved after extirpation of the forebrain including the basal ganglia, but coordination of instinctive acts is disturbed. Male fishes without forebrain carry out all instinctive acts of reproduction including nest building movements but do not complete the nesting actions at the same place, so that no nest is built [Schönherr (228)]. Olfactory lesions alone do not interfere with nesting behavior. Male sticklebacks without forebrain are less inclined toward

fighting although the fighting movements are undisturbed. Hypothalamic lesions produce more serious interference with reproductive instinctive behavior. We may conclude from Schönherr's experiments that in fishes lower brain-stem centers are able to mediate the elements of instinctive actions, but that coordination and integration of these instinctive acts depends upon the forebrain basal ganglia.

von Holst's (279) studies of optovestibular coordination in fishes have shown that a readiness for specific action (called 'motivation' or *Stimmung* by ethologists), caused by instinctive drives and appetites, may alter the central balance between optic and vestibular afferents. In male sticklebacks vestibular disturbances, compensated after unilateral utricular lesions, may reappear and result in rotation movements when a fighting situation is provoked by another male or when the fish hunts a prey. This coordination of instinctive drives and motor behavior apparently takes place in optovestibular centers of the lower brain stem. von Holst believes that fighting, hunger and other drives evoke an emotional readiness for action by facilitating vestibular impulses.

If we enlarge this hypothesis of emotional anticipation and readiness to include a facilitation of other extrapyramidal mechanisms in the brain stem probably through the reticular activation system, several clinical observations can be explained: the facilitation of various extrapyramidal hyperkineses by emotion and the *kinesia paradoxa* of parkinsonism, as well as the emotional decompensation of vestibular lesions resulting in vertigo.

MAMMALIAN BEHAVIORAL STUDIES IN RELATION TO EXTRAPYRAMIDAL CENTERS. Decorticate mammals exhibit certain instinctive actions, carried out by the basal ganglia and lower brain-stem mechanisms; feeding, drinking, fighting, rage, periodic sleep and sexual activity in females are preserved. By contrast human beings without cortex are more helpless when parts of the basal ganglia with the pallidum are preserved because they cause rigidity. Mesencephalic human beings however may have much better motor coordination and show a series of instinctive performances after certain afferent stimuli.

Certain emotional and feeding mechanisms of infants at various ages have been described by Peiper (207). By the study of normal and anencephalic children, it has been established that sucking, oral adversion and yawning (with stretching) can be carried out by mesencephalic and rhombencephalic structures. Some of the responses of Gamper's mesencephalic human being (67) are shown in figure 19. It was able to follow by turning the eyes and the head upwards and sidewards after attention was aroused and it made coordinated snapping movements towards the finger (fig. 19*c*). These mechanisms are not simple 'reflexes' but instinctive innate patterns which are elicited by sensory sign-stimuli. This creature was able to cry and to yawn. It displayed oral adversive movements, especially after stimuli near the mouth, so that its feeding behavior approached that of a normal child. Periodic alterations of activity resembling sleep and wakefulness as well as yawning and its associated stretching occurred (fig. 19*a*). In contrast to normal infants with intact thalamus and pallidum, however,

FIG. 19. Instinctive behavior and oral automatisms in Gamper's mesencephalic human being. *a:* Yawning with spreading of arms. *b:* Oral adversive movements after touching the lips with deviation of eyes. *c:* Coordinated gaze and snapping movements after finger was removed. *d:* Spontaneous sucking of own hand. *e:* Oral adversion to the left side with deviation of head and eyes and tonic neck reflexes in the arms. [From Gamper (67).]

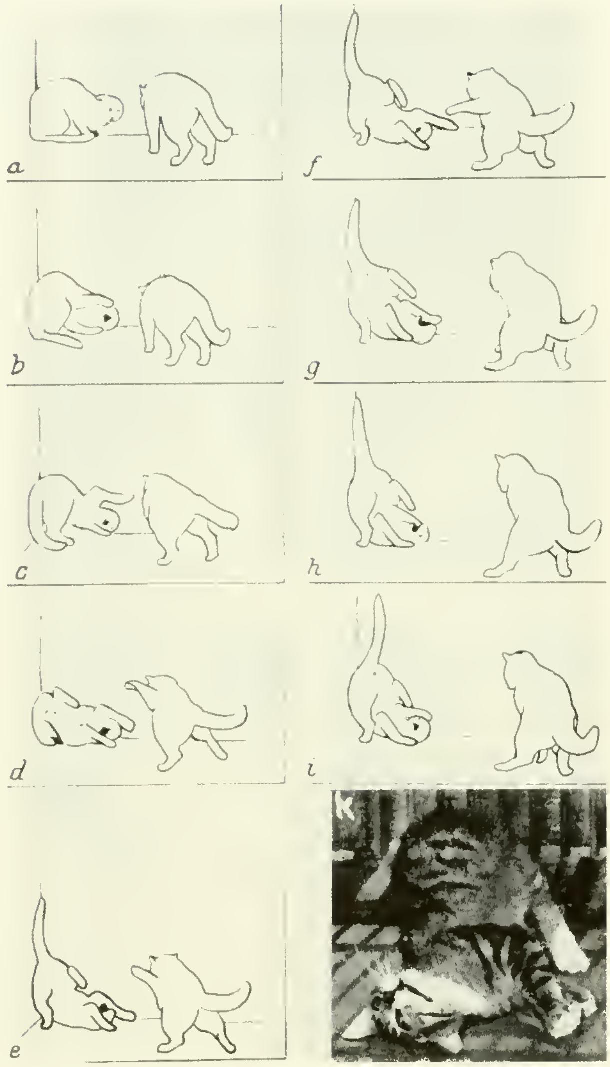

FIG. 20. Spontaneous rotatory movements of cats as integral parts of instinctive behavior. *a* to *i*: Sudden rotation of a defending male cat during fight. *k*: Slower rotatory turning movements of a female cat in heat during sexual play before mating. The head precedes a clockwise rotation and rolling movement. [From Leyhausen (160).]

there was little spontaneous activity. Left alone the anencephalus remained mostly in a drowsy state from which it could be aroused by sensory stimuli.

Rolling movements are integral parts of certain types of instinctive behavior, such as appear in male cats fighting each other or in female cats during sexual play. Examples taken from the studies of Leyhausen (160) appear in figure 20. These movements are doubtless similar in nature to the rotatory movements of the head and body which Hess obtained in cats by stimulation of the diencephalon. (fig. 10). Their appearance in instinctive activity apparently depends on emotional release.

Very little is known about the role of the extrapyramidal motor system in conditioned behavior. Stevens & MacLean (manuscript in preparation) found that low-frequency stimulation of the caudate nucleus in cats caused a failure of conditioned avoidance responses whereas high-frequency stimulation caused circling but did not alter the conditioned reaction. Brady (13) observed elimination of conditioned fear responses when cats indulged in self-stimulation of the caudate nucleus. Recent experimental evidence has shown an important role for the nonspecific activation system in conditioned responses.

Endocrine Influences on Extrapyramidal Mechanisms

That the extrapyramidal motor centers are related to the endocrine system is indicated by some clinical and experimental observations, but their mechanism is still obscure. An influence of the sex hormones was suggested by the observation of Simons (235) that tonic neck reflexes in a female hemiplegic were diminished or abolished during menstruation. Olds (203) observed that in self-stimulation experiments with electrodes in the caudate nucleus, castrate rats responded only when the androgen level was kept adequate. Clear experimental evidence for hormonal action on extrapyramidal structures is available only for lower pontobulbar centers. Dell *et al.* (38) have established the activating influence of epinephrine on the reticular formation. A clinical parallel may be the increase in the tremor of Parkinson's disease produced by epinephrine, as described by Barcroft *et al.* (11). The physiological meaning of these interesting and puzzling observations still remains to be investigated.

Electrophysiology of Basal Ganglia

As stated above, the application of classical methods of localized stimulation and extirpation to the basal ganglia in animals was rather disappointing. New hope for experimental investigation of basal ganglia arose when the recording of brain potentials was then applied to the extrapyramidal system in the deeper brain structures. However, information so obtained has been rather limited and its physiological interpretation not very illuminating.

Gerard *et al.* (68) first used the Horsley-Clarke apparatus for picking up potentials from various

subcortical structures but did not pay special attention to extrapyramidal centers. Spiegel (238) recorded potentials from the thalamus. Jung & Kornmüller (136, 137) made a systematic study of the brain potentials of the caudatum, putamen and thalamus of rabbits, cats and monkeys, using a modified Hess' technic of implanted electrodes. In unanesthetized rabbits and cats they found periodic spindle-like brain waves appearing in the striatum nearly synchronized with the contralateral striatum, the medial thalamus and the motor cortex. After sensory stimuli, flattening suggestive of desynchronization was recorded in the striatum, motor cortex and medial thalamus simultaneously with evoked rhythmic waves in the hippocampus. Accordingly a functional coordination of these different brain structures was assumed to exist although the anatomical connections remained obscure, especially between the motor cortex and the striatum. Jung & Kornmüller (137) suggested in 1938 that bilateral connection of striatum and motor cortex was induced by a 'third brain structure.' In these early times the nonspecific thalamoreticular system was unknown. One may now assume that this coordination of periodic brain potentials and desynchronization can be regarded as a function of the nonspecific activation system. This assumption is supported by the findings of many authors [Jung & Tönnies (138), Stoupel & Terzuolo (248), Umbach (261, 262)] that stimulation of the caudate elicits trains of cortical waves resembling the recruiting potentials and that these waves show highest amplitudes in the motor fields. The bilateral synchronization of potentials found in the left and right caudatum of cats and rabbits was explained by Jung & Kornmüller as the consequence of a common pacemaker. Direct induction by the contralateral caudate was rejected because convulsive potentials did not spread from one caudate nucleus to the contralateral one and because anatomical commissures between the striata were lacking.

When barbiturate anesthesia was given, Jung & Kornmüller found the large slow potentials appearing in the caudatum before they were seen in other brain regions. This was confirmed later by Schneider and co-workers (227) in a systematic study of narcosis. As in animals, the spontaneous rhythms of the striatum and pallidum in man do not differ essentially from the cortical brain rhythms. Hayne *et al.* (93) described somewhat faster alpha-waves from the human caudate than from the cortex. The putamen, pallidum and surrounding structures had similar frequencies and amplitudes; the main source of the potentials was found in the head of the caudatum and the putamen. Knott and co-workers (151) found early changes in caudate electrical activity at the onset of sleep as did Hodes *et al.* (116) in the monkey.

Our own experience during stereotaxic operations in man failed to show regular or characteristic changes of electrical activity of the basal ganglia in extrapyramidal diseases. But Spiegel and co-workers (244) observed a case of posthemiplegic athetosis having brain waves of low amplitude in the contralateral caudate.

Alterations of subcortical electrical activity under the influence of drugs other than anesthetics were described in cats with and without lesions of the basal ganglia by Baker *et al.* (10), and Baird and his colleagues (9), and in a few cases of extrapyramidal diseases by Spiegel *et al.* (239). Brain wave slowing after chlorpromazine, meprobamate and bulbocapnine was observed in the striatum and pallidum, chiefly in the caudate nucleus. Increased sensitivity of the pallidum to drug action was observed after homolateral caudate lesions by Baird and co-workers (9).

Kennard & Nims (146) found that lesions of the head of the caudate in monkeys were followed by changes of cortical potentials showing more intense 'hypersynchrony' of the alpha waves. Combined lesions of the motor cortex and the basal ganglia caused the most marked changes.

The effects of electrical stimulation of the basal ganglia have been studied. Jung & Tönnies (138) found incidentally that intralaminar thalamic stimulation evoked potentials in the caudatum and hippocampus with lower threshold than in the isocortex and that caudate stimulation evoked recruiting-like responses in the isocortex and allocortex. Ajmone-Marsan & Dilworth (2) recorded recruiting responses in cat caudate nucleus after stimulation of the nonspecific thalamic nuclei. Stimulation of the caudate produced recruiting-like responses in the cortex of shorter latency. Lesions of the caudatum affected only slightly the cortical recruiting response but did not abolish it. They concluded that the striate system does not have an 'active' role in the production of the recruiting response.

In cats Spiegel *et al.* (239) found a close relationship between the nonspecific thalamus, the caudate nucleus and the pallidum after thalamic stimulation. Recruiting potentials of the striopallidum were more constantly (but not exclusively) obtained from the nonspecific thalamic nuclei than from the association

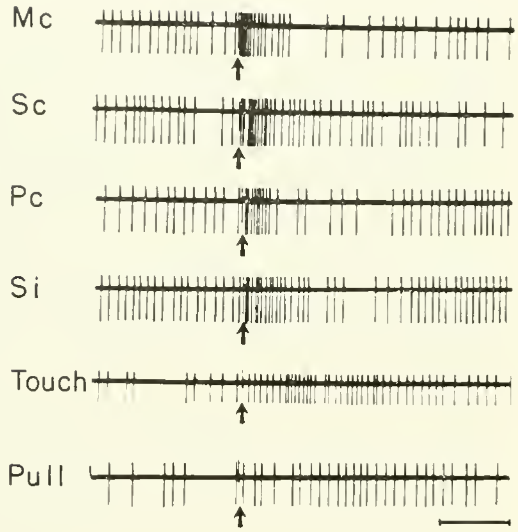

FIG. 21. Neuronal activity in the putamen following various afferent stimuli. Effects of single shock stimuli (7 v.; 0.1 msec.) at *arrow* to contralateral median (*Mc*), contralateral sciatic (*Sc*), contralateral peroneal (*Pc*) and ipsilateral sciatic (*Si*) nerves. *Below:* Responses elicited by lightly touching fur at base of tail (*touch*) or by stretching the contralateral gastrocnemius muscle (*pull*); application of such stimuli occurred approximately at *arrow*. Downward deflection represents a positive signal and time calibration indicates 500 msec. [From Segundo & Machne (231).]

or the specific relay nuclei. In man intralaminar thalamic stimulations induced recruitment waves in the pallidum.

Conversely pallidal stimulation may induce recruitment waves in the human cerebral cortex mainly in the homolateral hemisphere [Hassler (85, 86), Umbach (261)] (fig. 18). Spiegel & Wycis (243) and Umbach (261), however, found recruiting phenomena and waxing and waning of cortical responses following pallidal stimulation less constantly than after thalamic stimulation. A clear distinction between recruiting and augmenting potentials as described by Morison in cats is not always possible in man.

Ajmone-Marsan & Dilworth (2) and Shimamoto & Verzeano (233) described recruiting waves in cats after caudate stimulation at a rate of 8 per sec. similar to those appearing after stimulation of nonspecific thalamic nuclei. The experiments of Umbach (262) in cats (*encéphale isolé*) showed that caudate stimuli of low frequency cause constant spindle bursts in both caudate nuclei, the motor cortex (mainly homolateral), hippocampus and intralaminar thalamus. During the slow wave in the caudatum which precedes a spindle burst a silent period occurs in the same structures which show spindles after caudate stimulation. The effects of caudate stimulation can be conditioned by stimulation of the reticular formation. The electrical activity of the caudate prefers slow frequencies of 5 to 7 per sec. and even in convulsions does not show higher frequencies than 15 to 25 per sec. During clonic convulsions the caudate shows early rhythmic slow waves and silent periods preceding other brain regions. This may indicate a special role of the caudate in clonic convulsions. Whether the caudate can induce the rhythm of clonic discharges by intermittent inhibition as suggested by Jung (131) is not yet clear. Electrical stimulation of the caudatum sometimes but not regularly can suppress convulsive activity in the rhinencephalon and isocortex. Umbach's experiments give some additional evidence for an inhibitory function of the caudate which tends to restrain excitation processes in the brain.

Microelectrode recording within the lenticular nucleus and the claustrum of the cat was carried out by Segundo & Machne (231). Their results are of special importance for the afferent projection of different modalities to the higher extrapyramidal centers. They found that approximately two thirds of the neurons of the putamen responded to various somatic sensory stimuli mainly from skin and muscles, as shown in figure 21. Activation as well as inhibition of neurons was encountered. Inhibition (cessation of unit firing) was apparent only in neurons of the putamen, while activation with different latencies was found in both pallidum and putamen. The temporal pattern of response was distinctive for each type or location of afferent stimuli. Association of somatosensory and vestibular effect was described as the most common type of convergence on single neurons of pallidum and putamen. One third of these neurons reacted to vestibular stimuli by increase or decrease of discharge. Effects from vagus nerve stimulation were also found in the putamen. Olfactory, acoustic or optic effects were exceptional but occasionally also resulted in convergence with somatosensory afferents.

Segundo & Machne on the basis of their findings have suggested that the motor functions of the striatum and pallidum include a participation in the sensory-motor regulation of complex behavior. These investigations are a promising starting point for further researches on single neurons of the extrapyramidal system that will give us a more detailed insight into the functions of the basal ganglia.

CONCLUSIONS

A synopsis of the many observations and experiments collected in the preceding pages proves rather disappointing. To draw general physiological conclusions from the various experimental and clinical facts known about the extrapyramidal system is difficult for three reasons: *a*) the arbitrary anatomical definition of the extrapyramidal motor system in the basal ganglia limits consideration of functional motor correlations; *b*) the marked divergence between the symptomatology of human extrapyramidal disorders and those experimentally produced in animals; and *c*) the hazard of making deductions from the results of lesions, stimulations and electrical recordings in limited regions. With these difficulties in mind we may try to draw some general conclusions.

Four recent trends of research have contributed importantly to our knowledge of the extrapyramidal motor system and of the functions of the basal ganglia: *a*) the discovery by Hess (100–105, 108) of direction-specific movements evoked by diencephalic and mesencephalic stimulation in freely moving cats, and the localization by Hassler (89) and by Hassler & Hess (91) of the nuclei and tracts in the brain stem mediating these responses; *b*) the application of modern neurosurgical techniques, particularly stereotaxic instrumentation by Spiegel, Wycis, Talairach, Hassler, Riechert, Narabayashi, Leksell, Cooper and others, to problems of extrapyramidal function (92), the results of which have completely changed our concepts of the origin of the parkinsonian syndrome; *c*) the discovery of the motor control of muscle proprioceptors by Sommer (236) in man, of the gamma motoneuron system in animals by Leksell (158) and Hunt & Kuffler (120), and of the supraspinal control of this system by Granit & Kaada (72) in which extrapyramidal, cerebellar and pyramidal neuronal circuits play an important role; and *d*) the development of microelectrode studies of single neuron units in the basal ganglia, begun by Segundo & Machne (231), through which the rich variety of afferent impulses converging on extrapyramidal centers is now being explored.

Different Organization of Extrapyramidal System in Man and Animals

Although the gap between animal experiments and neurological disorders in man cannot be bridged, these divergences clarify some essential features of the physiological and anatomical organization of the human motor system. The different anatomical development of extrapyramidal structures in man and animals, the development of upright gait, the preponderance of the human pyramidal system and, finally, the different arrangement of the motor mechanisms for postural supporting reactions and automatic movements are factors at least partially accounting for the differences observed.

Characteristic features of human extrapyramidal disorders are the various hyperkinetic syndromes which are unknown or less apparent in animals. This demands a general explanation of hyperkineses on a physiological basis. Such an explanation can now be given. According to Hess, the antagonistic 'tonic' forces of the central motor regulation systems represent latent motion but are normally balanced. Manifest movements occur only after this balance has changed by physiological order or pathological disorder. A disequilibrium due to inhibition or to a loss of one of several balanced forces in the central nervous system may result in unintentional movements in the opposite direction. We assume that the more differentiated and delicate balance of human motor functions, subserving manual manipulation and regulating upright gait, makes them also more liable to disorders resulting in involuntary movements.

Mechanism of Extrapyramidal Disorders

Hyperkinetic symptoms probably similar in monkeys and man can be produced by lesions of the subthalamic nucleus and its surrounding pathways which result in hemiballism and hemichorea. Postural tremor can be evoked in monkeys and less consistently in cats after midbrain tegmental lesions, but parkinsonian syndromes accompanying disease of the substantia nigra in man cannot be reproduced in animals. Although parkinson-like symptoms are described in monkeys following large bilateral mesencephalic lesions overlying the nigra which were diminished by destruction of the caudal pallidum [Schreiner *et al.* (229)] as in human parkinsonism, the results of pallidotomy seem to be somewhat different in man and monkey.

Decerebration rigidity after midbrain transection or large tegmental lesions in animals is not comparable to the rigidity of human parkinsonism but is a syndrome revealing lower brain-stem motor mechanisms released after elimination of postural regulation by the higher extrapyramidal and pyramidal centers. Two different physiological mechanisms of decerebrate rigidity depend on hyperactivity of the

alpha and of the gamma systems of motoneurons. Alpha hyperactivity occurs after anemic decerebration, gamma hyperactivity after midbrain transection. Although the gamma system may show certain disturbances in human parkinsonism, these are opposite to that in the decerebrate state and the conditions in animals and man after midbrain lesion cannot be homologized.

In man lesions of the higher levels of the extrapyramidal system, especially the striatum and subthalamic nucleus, induce contralateral hyperkinetic movements, such as those of hemiballism and chorea. Combined lesions of the higher extrapyramidal centers in the telencephalon and diencephalon cause athetotic and dystonic syndromes. Lesions of lower extrapyramidal centers in the midbrain, especially in the nigra, cause parkinsonian tremor, rigidity and akinesis.

Pathological Manifestations and Normal Function of Extrapyramidal Structures

To attribute special functions to special nuclei of the extrapyramidal system would be a crude simplification. Nevertheless an effort to suggest the role of the structures of the extrapyramidal system in motor coordination should be made although only with caution.

The striatum (caudatum and putamen) receives afferent impulses from many different receptors, but the main afferent pathways come from the centromedian nucleus of the thalamus. Striatal lesions in man result in hyperkinesis accompanying intentional movements as in chorea. In animals striatal stimulation causes contralateral deviation or general inactivation. Lesions in cats and monkeys are followed only by slight hyperkinesis and surprisingly few defects of longer duration. The coordinating function of the striatum seems to be very complex and may be tentatively circumscribed as regulation of intentional movements by suppressing and screening additional motor mechanisms in some functional association with the nonspecific thalamoreticular system regulating sleep and general activity.

The role of the pallidum in extrapyramidal disorders has had to be revised as a result of recent experiences with stereotaxic lesions in man. The old conception that pallidal lesions cause muscular rigidity was not confirmed; stereotaxic pallidotomy in parkinsonian states and other extrapyramidal diseases has the opposite effect of diminution of muscular rigidity. Electrical stimulation of the human pallidum does not result in any direct motor effects but causes a partial blocking of voluntary movements and arousal or adversive effects. Destruction of the pallidum causes a general inactivation or sleep syndrome of short duration and a diminution of muscular tone at the contralateral side of the body of long duration, as well as of rigidity in parkinsonism. The functional role of the pallidum may be tentatively designated *a*) increasing the tonic background of intended and automatic movements, and *b*) general activation in coordination with the thalamoreticular system.

The corpus subthalamicum of Luys has two-way connections with the external pallidum. Lesions of this nucleus in monkeys and man result in contralateral choreiform or hemiballistic movements. The function of the subthalamic nucleus cannot be defined exactly but may be similar to that of the striatum by restraining motor activity of the contralateral side in collaboration with the activating influence of the pallidum.

The centromedian nucleus of the thalamus seems to be the main crossroad for the coordination of the nonspecific activating and the extrapyramidal motor system. Electrical stimulation may cause sleep or arousal effects in animals and man, depending upon the frequency and strength of stimulation. Control of the general motor patterns of attention and arousal may be tentatively ascribed to the function of this nucleus.

The role of the red nucleus in the extrapyramidal motor system is still obscure. The fact that, while in the lower animals it is predominantly magnocellular and gives rise to the rubrospinal tract, in man it is mainly parvicellular, and originates the large descending central tegmental tract and renders generalizations concerning its functions hazardous. In cats stimulation of the magnocellular part of the red nucleus and rubrospinal tract causes raising of head and foretrunk. Although adequate evidence is lacking, the anatomical connections seem to indicate that the parvicellular red nucleus of man exerts a controlling function by negative feedback to the cerebellum via the central tegmental tract and inferior olive, so regulating upright posture and gait and making possible the postural corrections required for the telekinetic or intentional motor actions.

Selective destruction in man of the substantia nigra, which has connections with the striatum, cerebral cortex and reticular formation, causes the parkinsonian syndrome. Human tremor shows all the phenomena of relative coordination, described by von Holst (278) in the fin movements of fishes (fig.

15). Tremor may be facilitated by impulses arising from the pallidum and the afferent pathways to the motor cortex, and conducted by the corticospinal tract and other extrapyramidal pathways. We regard the essential mechanism of tremor as a release of rhythmic antagonistic movements occurring in lower spinal or bulbar levels.

Lower Centers of Statokinetic Regulation in the Brain Stem

The substrate of Hess' direction-specific movements of eyes, head and trunk resides in the lower extrapyramidal structures of the diencephalon and mesencephalon, as shown in figures 8 and 9. Stimulation in the cat of these structures results in rotatory, raising, lowering or turning movements, while destruction results in positions which are the mirror image of those resulting from stimulation (fig. 10). Rotatory movements around the longitudinal axis are obtained from the interstitial nucleus, from its fiber connections and from medial fibers of the brachium conjunctivum. The efferent paths run through the interstitiospinal tract. Raising movements around the bitemporal axis are obtained from the prestitial nucleus. The efferent paths go through the medial longitudinal bundle and rubrospinal tract. Lowering movements around the bitemporal axis are obtained from the precommissural nucleus and its descending tract to the tegmentum. Ipsiversive turning movements in the horizontal plane around the vertical axis are obtained from the region of the mesencephalic reticular formation supplied by ipsilateral vestibuloreticulothalamic fibers and by the vestibulothalamocortical system. These parts of the reticular formation seem also to contain the efferent mechanisms of contraversive cortical and subcortical adversive systems, after crossing in the mesencephalon.

These results are obtained only in quadruped animals. The organization of these systems is essentially different in man who has developed a quite different relation between head position, eye movements and trunk axis in his upright posture. The common extrapyramidal disorder of oblique head turning in human torticollis and torsion dystonia probably represents a regression to lower phylogenetic mechanisms released by asymmetrical disturbances of higher centers regulating head and body posture.

Extrapyramidal Cortical Areas

Somatomotor movements obtained by stimulation of the cerebral cortex after complete destruction of the pyramidal tract were among the first extrapyramidal motor functions demonstrated experimentally. However, the neurophysiological significance of the so-called 'extrapyramidal areas' of the cerebral cortex (areas 6, 8 and 4s) still remains problematic. Further, the existence of a component of the pyramidal tract arising in extrapyramidal areas seems rather certain. On the other hand, adversive movements after stimulation of area 6 can be obtained without connections of this area with area 4 and after interruption of the pyramidal tract. The complex integration of motor activity requires close coordination of the extrapyramidal system with the pyramidal system in the cerebral cortex, the cerebellum and the peripheral receptors, particularly in man. Only in the lower forms does the extrapyramidal motor system, together with the reticular activating system and spinal mechanisms, seem to be sufficient to integrate instinctive motor behavior.

Afferent Mechanisms

Apparently the proprioceptive influences on the extrapyramidal centers necessary for their function act through the cerebellum. The various loops of neuronal chains illustrated in figure 12 seem to be the main anatomical mechanisms. Besides the cerebellar contribution, direct proprioceptive influence must also be postulated for the various direction-specific movements of the head and eye. At least cervical joint and labyrinthine receptors signaling the position of the head must operate continuously as afferent regulators. Many other afferent impulses apparently impinge on the neurons of the higher extrapyramidal centers, as recent unit records from the striatum have shown.

Efferent Mechanisms and Cooperation with Motor Cortex and Cerebellum

How the efferent pathways of the extrapyramidal motor system are coordinated with the pyramidal and cerebellar systems can not yet be formulated with confidence. A tentative scheme suggested to Hassler in 1956 by the anatomical connections is shown in figure 12. The most important efferent pathways to the spinal motor horn seem to be the rapidly conducting reticulospinal tracts. The cerebellum contains the principal mechanisms coordinating the different extrapyramidal centers with each other, with the reticular formation and with the cortical motor system. Special efferent structures of the cerebellum reach the reticu-

lar formation of the pons and the vestibular nuclei; others pass through the dentate nucleus to the upper levels of the thalamus and motor cortex. From there cerebrospinal fibers carry impulses coming from these circuits downwards. Thus the pyramidal tract may function as one of the efferent pathways of the 'extrapyramidal' system (fig. 12). Most of the coordinative integration of the extrapyramidal system at supraspinal levels is carried out in cerebelloponto-olivary centers, including the short neuron systems of the reticular formation.

Thus the complex motor regulatory influences of the basal ganglia are exerted through the cerebellum and the motor cortex. The main descending path in the brain stem for these cerebellar circuits is the central tegmental tract from the red nucleus to the reticular formation and inferior olive. The result of this integration in short and long chains of neurons, coordinated with vestibular and cortical impulses and with cervical proprioceptors, is transmitted to the anterior horns. In parallel with the descending reticulospinal tracts, the interstitiospinal and vestibulospinal pathways influence the motor horn cells mainly for the direction-specific movements of head and body. The rubrospinal tract (from the magnocellular red nucleus) has no significance in the human. The efferent pathways of the parvicellular red nucleus are relayed through the central tegmental tract in the reticular formation [Weisschedel (291)] or coordinated with cerebellar circuits through the inferior olive.

At the spinal level the efferent extrapyramidal impulses carrying downwards the integrated and simplified result of cerebral coordination cooperate with the propriospinal interneuron systems, fed by extero- and proprioceptive afferents from the periphery. Impulses in the long cerebrospinal tracts end mostly on spinal interneurons. Direct endings on alpha motoneurons, if existent, are of little significance, but endings on gamma motoneurons may be more important. This spinal sensorimotor coordination cannot work properly without the external loops of the gamma motoneurons, regulating proprioceptive afferent flow from the muscle spindles. By this convergence of neuronal circuits the highest motor centers are able to control motor readiness and to command motor performances at the lowest level of peripheral motor effectors.

The relation of higher extrapyramidal centers to spinal reflexes has not yet been sufficiently investigated. Control of the gamma motoneuron system and muscle spindles over two separate pathways from the reticular formation seems to be a probable function of lower extrapyramidal structures.

The role of the extrapyramidal system in posture and locomotion is clarified by application of Hess' dynamic interpretation in terms of his concept of 'teleocinetic' and 'ereismatic' motility. Normal posture is the result of a dynamic equilibrium of central antagonistic forces continuously active in the waking state and controlled by afferent impulses. On the lower motor mechanisms, mainly dependent upon labyrinthine and cervical proprioceptive influences, is superimposed a mesodiencephalic coordinating apparatus for body posture showing an elaborate direction-specific differentiation, closely integrated with the cerebral cortex and operating in the three dimensions of space. The physiological mechanism of 'ereismatic' supporting motility seems to be primarily proprioceptive but is regulated in anticipation of action via the gamma system and its extrapyramidal control. However, we are still ignorant about the mechanisms of motor anticipation in the higher extrapyramidal and cortical centers.

The relation of extrapyramidal functions to instinctive behavior is revealed by the findings of comparative physiology and some reactions of decorticate mammals. In birds having a highly developed striatum and little cerebral cortex, the upper and lower striatum can regulate their behavior and they can even exhibit some learning without the cerebral cortex. Complex instinctive actions as mating and nesting require the hyperstriatum but not the cortex. Simpler components of their feeding, drinking, fighting and courting behavior are possible without the cerebral cortex and hyperstriatum but only if the ectostriatum and mesostriatum are intact.

Relations of the extrapyramidal system to the thalamoreticular regulating system are suggested by phylogenetic, anatomical, electrophysiological and clinical evidence. Apparently extrapyramidal centers contain the motor mechanisms of attentive behavior and of the postural accompaniments of wakefulness in close coordination with the reticular formation of the brain stem. Phylogenetically the extrapyramidal centers seem to have been differentiated from the central core of the brain stem regulating motor behavior. The reticular formation is primarily a motor coordination apparatus. The psychological aspects of attention and consciousness are only secondary differentiations from this basic regulation of behavior.

In spite of the extensive literature on the extrapyramidal motor system we must confess that we know surprisingly little about the essential physiological

mechanisms of its functions and the coordinative action of its parts. Some of our conceptions were developed only from the interpretation of morphological data or from neuropathological observations and are not based on experiments. Fiber connections between different nuclei and the afferent and efferent pathways of basal ganglia give only limited indications of physiological functions. The efferent extrapyramidal mechanisms, especially, which probably consist largely of short chains of neurons, have not yet been worked out. The corticospinal (pyramidal) tract acts also as an efferent extrapyramidal mechanism, although this appears paradoxical at first sight. Very little also is known about the afferent input to the higher extrapyramidal centers from different receptor organs and about the role of these afferent influences in the coordination of motor activity. However, recent electrophysiological studies on single neurons of the striatum activated by different receptors provide a new approach to this problem and may help to elucidate the afferent aspect of the extrapyramidal system.

It is one of the purposes of this chapter to show the many gaps in our scientific knowledge in this field and to indicate where additional neurophysiological observations are needed. This may stimulate further research to solve at least some of the many physiological riddles of the functions of the basal ganglia.

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Spinal mechanisms involved in somatic activities

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CHAPTER CONTENTS

INTRODUCTION

ACTION MEDIATED BY THE SPINAL CORD differs depending upon what structures craniad to it retain functional continuity with it, and also to a degree depending upon the length of time it may have been isolated from these structures. Thus the decerebrate preparation displays prominently, indeed in exaggerated form, certain reactions that can be elicited only with difficulty, in fractional form, or not at all in the spinal preparation. But let the spinal preparation progress from the 'acute' to the 'chronic' status and certain reactions, previously submerged, are elicitable (76). Clearly the machinery was there yet inoperative in the acute phase. Still other reactions are more readily obtained in the acute spinal state than in the decerebrate, indicating that continuity with the brain stem brings to the spinal cord not only supportive influence but, perhaps equally, supressive influence. Submissive as the spinal cord is to higher centers it is nonetheless an organ in its own right; it contains the essential mechanisms for the reflex actions it mediates. Realization of this fact has increased immeasurably since the time when reflex action could be judged largely only by its external expression in muscle contraction. Today with the aid of delicate tests for excitability change in any motor nucleus of choice, one finds revealed the potentiality for action as well as action itself—expression, in subliminal form, of action that would take place were conditions appropriate.

Once the spinal cord has been isolated from supraspinal influence, specifically that of the brain, the power to initiate movement is lost to the animal and such movements as it executes are relatively stereotyped, dependent upon presentation of change in the external environment, and are in character related to the nature of that change. Mindful that the entities called reflexes normally are probably inextricably blended in the performance of the animal and so in a sense are artificial entities, one can remove each from its functional context for analysis and classify it. What then are some of these reflex entities? If one attempts, in the decerebrate

animal, to force the rigidly extended limb into a flexor posture, the limb resists the applied force by active muscular contraction. This in essence is the stretch or myotatic reflex (52). Upon increasing the force to a degree that might be supposed potentially harmful, the limb may suddenly give way and assume a new posture more in flexion. This happening is called the lengthening reaction (93), or inverse myotatic reflex (50). As the limb gives way, the limb opposite may increase its extensor posture, a reaction discovered by Philippson (79) and named after him—Philippson's reflex. If some part of a limb comes into contact with a source of hurt, that limb rapidly is removed from the source by a reflex of flexion, general in character, involving the several joints of the limb. Associated with this ipsilateral flexor reflex, and set in action by the same sorts of stimulation, is the crossed extensor reflex (92). A flexor stretch reflex is known and in operation plays a role in walking movements. There are others, the scratch reflex, hand-foot reactions and so on; but it is sufficient when concern is with principles to concentrate attention upon a few, the spinal mechanisms for which are reasonably well understood.

The reflex arc consists of afferent fibers that bring to the spinal cord information as to the environment, internal as well as external, and that reach the spinal cord by way of the dorsal roots; of motor fibers, emergent through the ventral roots, that in action provoke muscular contraction and movement; and of a mediate system of interneurons arranged in patterns, largely unknown, but certainly of varying complexity. The mediate system is engaged by all but one of the known spinal reflex reactions, that unique exception bring the stretch reflex (54, 55).

Entering into the spinal mechanism from the periphery are afferent fibers the action of which is destined to result in the relay of information to the higher centers. To what extent these are the same fibers as those which feed the local reflex mechanism is not reliably known. There are in turn descending fibers entering into the spinal mechanism from higher centers serving all manner of supraspinal influence over the final product of neural activity, motion. Thus the spinal cord is not only an organ in its own right but is also a major highway of liaison between the brain and the outer world.

CONSTITUTION OF AFFERENT PATHS

Dorsal roots contain myelinated fibers of all diameters from the largest, approximately 22 μ, to the smallest, approximately 1 μ. There are in addition unmyelinated fibers in profusion. A distinction of great functional import is seen if one considers not the entire gamut of afferent fibers gathered together in a dorsal root, but rather such aggregations of afferent fibers as appear severally in nerves to muscles and nerves to skin.

FIG. 1. Distribution with respect to diameter of the afferent fibers in a 'demotored' muscle nerve (*heavy line*) and in a cutaneous nerve (*faint line-shaded area*). The pile of fibers centered at 17 μ, unique to muscle nerves, is termed Group I. Group II includes the pile of fibers centered about the 8 μ peak, and Group III those about the 3 μ peak. [From Lloyd (60).]

Figure 1 illustrates the distribution with respect to diameter of myelinated afferent fibers in a typical 'demotored' muscle nerve (63) and a typical skin nerve (29). There are three peaks of numerical preponderance; one, located at approximately 17 μ, consists of a group of fibers unique to the muscle nerves. The other peaks, at approximately 8 μ and 3 μ are present in both muscle and skin nerves. In order of decreasing magnitude the fibers gathered about these three peaks are designated, respectively, Group I, Group II and Group III (54, 63). Among skin afferent fibers those designated Group II correspond essentially to the alpha and beta fibers and Group III to the delta fibers of earlier description (24). The present terminology, yielding in priority with respect to skin nerves, is the more convenient when reflex action is the subject under review.

Afferent fibers from joints play an important role in somatic activities, although they have not been studied as intensively as have the other sorts. They are distributed with respect to diameter in much the same way as are skin afferent fibers.

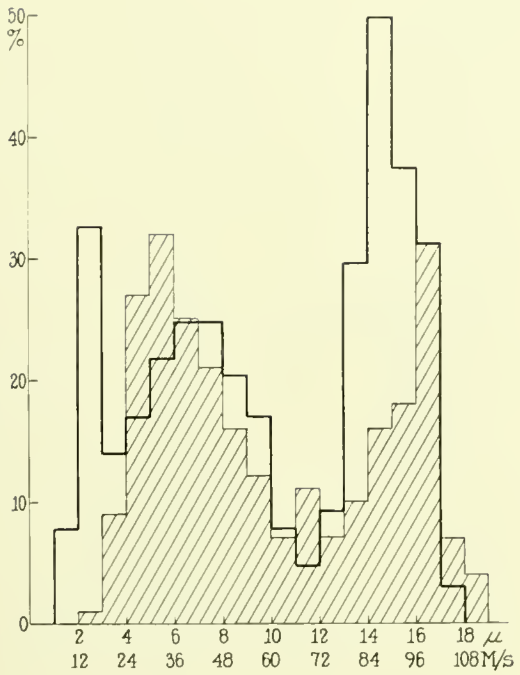


FIG. 2. Distribution with respect to conduction velocity (and hence to diameter) of afferent fibers from A-type muscle receptors (muscle spindles). The *heavy line* plots the distribution with respect to diameter of the afferent fibers of the soleus muscle (Lloyd and Chang). The *faint line-shaded area* plots the distribution of A-type afferent fibers according to physiological test. *Ordinates:* number of fibers in each 1 μ category of diameter. *Abscissae:* diameter in μ and conduction velocity in meters per sec. [From Hunt (37).]

PERIPHERAL ORIGINS OF AFFERENT FIBERS

Muscle Afferent Fibers

Muscle spindles and Golgi tendon organs account for the great majority of receptors in mammalian muscle. In addition there are 'free nerve-endings' in the connective tissues. The muscle spindle is rather complex in structure. An elongated spindle-shaped capsule contains several intrafusal muscle fibers innervated by motor fibers of small diameter (cf. 5, 86). Small bundles of afferent fibers enter the spindle; the large fibers, becoming flattened as ribbons, wrap themselves about the intrafusal fibers to form the primary or annulospiral endings. The smaller afferent fibers enter at some distance to form secondary, or flower-spray, endings, usually to either side of the primary ending. Muscle spindles are situated in the fleshy part of the muscle with their long axes parallel to the muscle fibers in such a way that traction on the muscle tendon puts them under tension while contraction of the muscle unloads the tension (27, 72–74).

Golgi tendon organs consist of a bundle of tendon fascicles enclosed in a fibrous capsule into which one or two myelinated afferent fibers penetrate, divide and terminate among the tendon fascicles. Tendon organs are put under tension both by external traction and by muscle contraction.

Muscle spindle afferent fibers can be activated by tendon traction or by stimulating the small motor fibers which leads to contraction of the intrafusal muscle fibers (39, 45, 51). When the muscle itself contracts, the spindles are unloaded and afferent fiber activity is reduced or ceases (72–74). Afferent fibers from tendon organs, whether quiescent or active according to the degree of initial tension, become active or increase their activity during contraction; they are not activated by small motor fiber stimulation (39). These differences permit identification of the peripheral receptor to which a given afferent fiber belongs (37).

By studying a large number of isolated afferent fibers, identifying each as to the type of receptor providing origin, and measuring conduction velocities, it has proved possible to make a quantitative accounting for the afferent fibers contained in the Group I and Group II bands of the fiber spectrum.

Figure 2 illustrates Hunt's findings (37) with respect to the afferent fibers of soleus muscle displaying functional origin in the A-type (muscle spindle) receptors. These account for some 60 per cent of the Group I fibers and all of the Group II fibers. The Group I fibers of spindle origin have a distribution skewed toward the larger diameter members of the histological Group I band. This was not so marked in the medial gastrocnemius which also was studied by Hunt. Much reason exists for supposing the Group I spindle afferent fibers, henceforth called Group IA, derive from the primary, or annulospiral, endings and that the Group II spindle afferent fibers derive from the secondary, or flower-spray, endings. No stringent rule can be applied to the region of the valley between the Group I and Group II peaks; in short the division between Groups I and II is arbitrary. In general the relative numbers of muscle spindle afferent fibers in the two groups is not out of line with the relative numbers of primary and secondary endings as observed in histological survey (5).

Figure 3 illustrates Hunt's findings concerning the distribution with respect to velocity (and hence by a factor to diameter) of the afferent fibers arising, according to functional test, in Golgi tendon organs.

These afferent fibers, henceforth called Group IB, can be considered as falling exclusively in the Group I band with the preponderance toward the lesser diameter members of that band.

Actually the question of IA and IB fiber distributions in the Group I band is in a state of utter confusion, and the interpretation of experiments, even in some instances the results of experiments, is highly controversial. A definitive statement cannot be made at this time. To facilitate discussion of the situation it should be noted that Group I afferent fibers include those that form monosynaptic reflex connection for mediation of the myotatic reflex (54; see also below), and that it is generally conceded that the muscle spindle is the myotatic reflex receptor.

The terms Group IA and Group IB first came into use after Kuffler & Hunt (40, 44) proved that the Group I band contained afferent fibers from the two sorts of receptors, called A and B after the original terminology of Matthews (72–74). Prior to that it was known that the Group I band contained the monosynaptic afferent fibers, and it was only at that time that it became clear that the band contained afferent fibers serving another reflex pattern (50, 59). Subsequently Rall (80) studying the input-output relation of the monosynaptic reflex of gastrocnemius found the monosynaptic reflex output to be maximal at 60 to 70 per cent Group I input, an observation that has repeatedly and consistently failed of confirmation in the spinal preparation. For instance, in spinal animals Hunt (38) and Lloyd & Wilson (69) have shown the monosynaptic reflex output to increment progressively from reflex threshold until measured Group I input is maximal, this is in accord with the distribution of muscle spindle afferent fibers of the gastrocnemius. Then Bradley & Eccles (9) described the triphasically recorded conducted afferent Group I spike of biceps-semitendinosus and quadriceps, but not of other muscles, as a 'double negative spike.' These two peaks, in order of latency, were designated IA and IB and it was assumed that the A-type afferent fibers (muscle spindle) occupied the first peak and that B-type fibers (tendon organ) occupied the second.

A curious aspect of this bifid allegedly Group I triphasic spike is its inconstant occurrence. Bradley & Eccles report it as being 'an almost invariable finding,' whereas Laporte & Bessou (47) describe it as having been encountered only after many experiments. Lloyd & McIntyre (66) did not encounter bifid spikes but, in the light of the foregoing, may

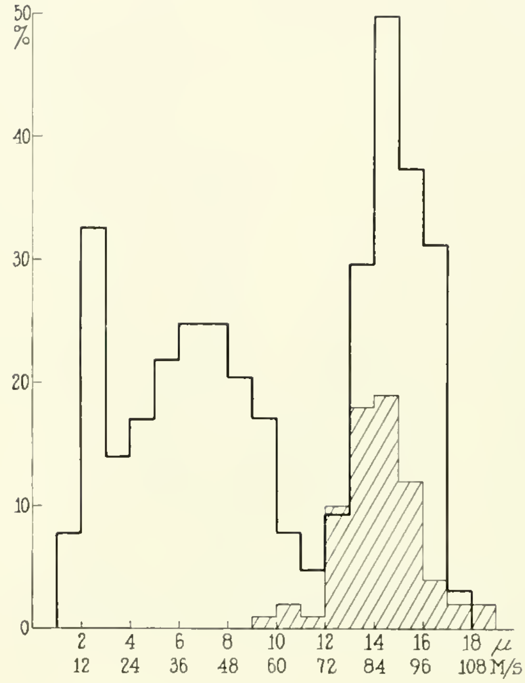


FIG. 3. Distribution with respect to velocity (and diameter) of afferent fibers from B-type muscle receptors from the soleus compared with the histological afferent fiber spectrum. Manner of construction as in fig. 2. [From Lloyd (60); after Hunt (37).]

not have persisted long enough. Another curious aspect is that the threshold difference between IA and IB according to Bradley & Eccles is greater (1:1.52) than that between Group I and Group II (1:1.48) according to Brock *et al.* (10), which certainly is a result inviting caution in the interpretation and identification of the second peak of Bradley & Eccles.

It is unfortunate that Bradley & Eccles made no observations on Group II fibers of quadriceps and biceps-semitendinosus, for recordings illustrating response of the two groups would have facilitated interpretation.

Laporte & Bessou (47) report that most of the afferent fibers characterized as arising in spindles were located in their 'sous-groupe rapide' and those from tendon organs were in their 'sous-groupe lent' in the few instances in which they found bifid spikes. Unfortunately there is no indication that they followed the rigid criteria established by Hunt (37) for representative sampling, a most essential aspect for quantitative study of units (61). Certainly the rigid categorization by assumption presented by Bradley & Eccles cannot hold and one must reserve judgment

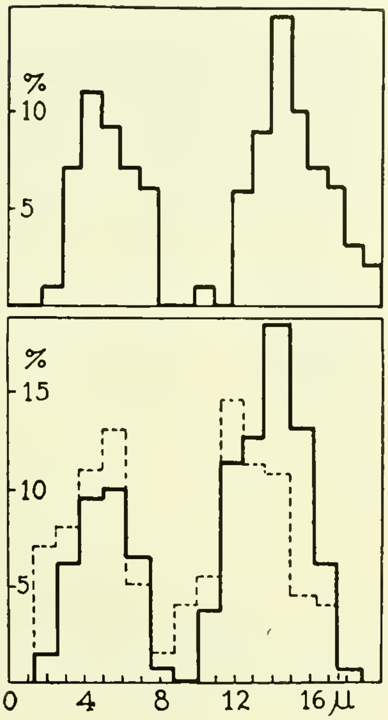


FIG. 4. Distribution with respect to diameter of motor fibers in a ventral root (*above*) and at two levels of deafferented gastrocnemius nerve (*below*). The *solid line* in the *lower part* of the figure represents the distribution of fibers in gastrocnemius nerve 50 mm from the muscle; the *broken line*, 8 mm from the muscle. The slight shift is accounted for by branching, the daughter fibers being of lesser diameter than their parent fibers. [Modified from Eccles & Sherrington (23).

on experiments in which a pure Group IA volley as defined by a spike potential is interpreted as being a pure Group IA volley in the sense of containing only spindle afferent impulses or monosynaptic reflex afferent impulses.

The Group III and unmyelinated fibers of muscle nerves have not as yet been identified as to peripheral origin. One presumes they arise as the free nerve-endings in muscle and, mindful of the fact that muscle can be the seat of pain, one surmises that these fibers may, as their counterparts in skin nerves do, serve the sensation of pain and provoke reaction of a sort associable with pain-producing stimulation.

Cutaneous Afferent Fibers

Skin afferent fibers serve several modalities of sensation: touch, pressure, warm, cold and pain. No very clear relation exists between the various segments of the fiber spectrum and the modalities represented (28). For the most part the problems are properly considered in relation to the physiology of sensation. The reader is referred to the appropriate chapters in this work. One point of especial relevance to reflex physiology is the certainty that pain impulses are carried both by the delta fibers (Group III in terminology of reflexes) and by C fibers.

In terms of reflex action the cutaneous afferent fibers reveal no more clear relation to fiber distribution than do they in terms of sensation. There is upon electrical stimulation, in each circumstance, a dominant reflex action, but careful investigation can usually reveal admixtures—concealed reflexes in the words of Sherrington. In many instances the reflex actions produced by Group II and Group III fibers of skin nerves are similar; in some they differ. Also, reflex effect may differ according to the cutaneous area innervated by the nerve stimulated. In short, knowledge of the afferent channels for reflexes initiated from the skin is sadly deficient.

CONSTITUTION OF MOTOR PATHS

With respect to diameter, motor nerve fibers are clustered into two remarkably distinct peaks of preponderance (23) for which the designations large and small would appear to be suitable. Another terminology, widely used, refers to them as alpha and gamma fibers, respectively (32).

Figure 4 illustrates the disposition of motor fibers with respect to diameter. In a ventral root (fig. 4, top), the large fibers occur in a range from 20 μ to 12 μ and the small fibers in a range from 8 μ to 2 μ. In the thoracic and upper lumbar ventral roots, a much higher peak is found in the range of 3 μ, due to the presence of preganglionic sympathetic B fibers with which, however, the present discourse is not concerned.

As the motor fibers pass from ventral roots to their peripheral nerve extensions, axon branching takes place on an incrementing scale as the point of entry into muscle is reached. The daughter fibers are of lesser diameter than the parent fibers which leads to a shift in the fiber spectrum, apparently more marked among the large motor fibers than among the small. In exemplification of this fact are the diameter spectra at two levels of gastrocnemius nerve contained in figure 4 (bottom). The solid line is the fiber plot at 50 mm from the muscle, the broken line at 8 mm from the muscle.

In mammals, but not in the frog (44), the two groups of motor fibers are distinct in function as in caliber. The large fibers are motor fibers to skeletal muscle; the small fibers supply the intrafusal fibers of muscle spindles and by their action provide central control over muscle spindle afferent response, seemingly to adjust for the differing circumstances of tension under which the spindle must operate (44).

SPINAL LIAISON BETWEEN AFFERENT AND MOTOR PATHWAYS

Afferent fibers enter into the spinal cord and motor fibers depart therefrom. Between them they account for little of the bulk of neural tissue contained within the spinal cord. The vastly greater remainder consists of interneurons. Concerning the manner in which all these elements are organized, one can speak for the most part only in generalities, there being little known, with one notable exception, of precise linkages that may be peculiar to any particular reflex mechanism.

Distribution and Properties of Afferent Collaterals in the Spinal Cord

In figure 5 are to be seen the principle projections in the spinal cord of the primary afferent fibers. Those labeled *C* and *c* are directed into the nucleus proprius of the dorsal horn and the substantia gelatinosa Rolandi. These probably are concerned largely with the relay of activity to the great ascending tracts, although a distinct possibility exists that the latter nucleus is concerned with the relay of C fiber reflexes. The long collaterals *a* extend to the ventral horn, giving off in passing a few collaterals *b* to the intermediate nucleus. In the ventral horn at *B* these long collaterals have been shown to establish synaptic connection with motoneurons. Coming from the deeper aspect of the dorsal white column are dense bundles of collaterals *A* directed to the intermediate nucleus. It is evident that the intermediate nucleus is of great importance in reflex transmission, but the precise role it plays has been subject to varied opinion and can be regarded as controversial.

From a functional point of view the central projections of afferent fibers are considered to have some properties that differ from those of the parent fibers from which they arise. Rudin & Eisenmann (85) have

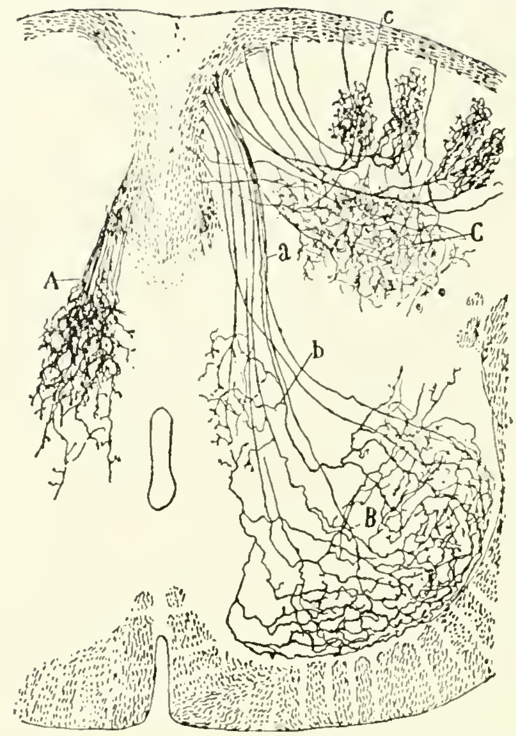


FIG. 5. Cross section of the spinal cord to illustrate the distribution of primary afferent fibers throughout the gray substance of the spinal cord. [From Ramón y Cajal (81).]

shown that the after-potential system of the fibers changes abruptly at the dorsal root-cord junction, the intramedullary segment displaying a large negative after-potential. As soon as the afferent fibers enter the spinal cord they branch and as branching takes place conduction velocity decreases. Precise measurements of intramedullary velocities are available only for some of the projections in the dorsal columns (66). In the much shorter collaterals into the gray substance, the decrease is dramatic and probably sufficient to account for most of the formal synaptic delay (56). What happens as impulses penetrate into the terminal regions of the collaterals is controversial. The notion that activity in those regions has an enduring quality unlike that of impulses in the parent fibers was brought to the fore by the experiments of Barron & Matthews (6). The alternative view that action in the terminals is as brief as peripheral axon spikes has been maintained vigorously (12, 21). Lloyd & McIntyre (65) showed that an enduring sink of current flow must exist in the terminal collaterals and that it would have the character of the potential change recordable in

FIG. 6. The 'presynaptic potential' recorded by means of an extracellular microelectrode. The initial deflection can be assigned to primary afferent fibers that pass by the electrode location. The prolonged negative deflection that follows represents an enduring change in the presynaptic endings of primary afferent fibers resulting from a single shock stimulus to Group I afferent fibers.

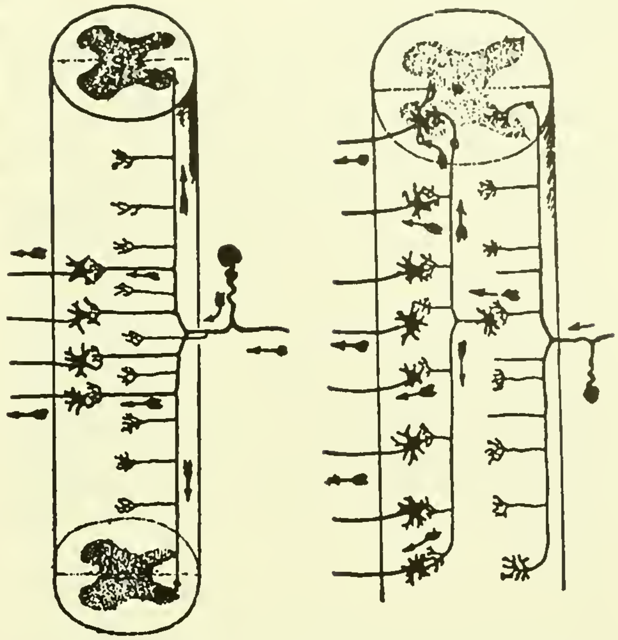


FIG. 7. Ramón y Cajal's diagram of the circumscribed reflex mechanism (*left*) showing the monosynaptic connection between the primary afferent fibers and motoneurons, and of the diffuse reflex mechanism (*right*) in which an interneuron is intercalated between afferent fibers and motoneurons. [From Ramón y Cajal (81).]

motor nucleus and presented in figure 6. For a variety of reasons, based on quantitative considerations, the potential illustrated must be considered an active presynaptic response rather than a passive and subliminal response of the secondary neurons. Suffice it to say that the properties of the primary afferent fibers change as they enter the cord and approach the terminal point at synapsis.

Circumscribed and Diffuse Mechanisms of Ramón y Cajal

One of the great generalizations concerning the functional organization of the spinal cord emerged as the culmination of Ramón y Cajal's study of the fine structure (81). It is presented in figure 7 on the left of which one finds his 'circumscribed' reflex mechanism in which afferent collaterals articulate directly with motoneurons in a restricted region to form a monosynaptic reflex arc. To the right is represented the 'diffuse' reflex mechanism in which interneurons are intercalated between afferent fibers and motoneurons. These interneurons were regarded as a means for diffusing activity over a wider field up and down the spinal cord.

Divergence and Convergence

It is probably true that the axons of most neurons in the central nervous system branch a number of times to form synaptic connection with a number of other neurons, as exemplified by the interneuron illustrated in the diffuse mechanism of Ramón y Cajal (fig. 7). This divergence is a feature in the functional organization of the spinal cord. Likewise one may make the generalization that many neurons receive, by convergence, synaptic connections from a variety of other neurons. It is immediately obvious that convergence is the necessary condition for integrative action in the nervous system. This truism in itself is cause for examining a little more closely the generality of convergence. One will grant convergence as a prime structural factor in organization of the motor systems, with the motoneuron, the final common path of Sherrington (90), the paradigm of convergent foci. But afferent systems that have been studied reveal a synaptic organization rather different from that of the motor systems, specifically that at the motoneuron. Output to the spinocerebellar tract from Clarke's nucleus is linearly related to input (66) and there is, among Clarke column neurons, no subliminal fringe (77). Except for the fact that output to a single synchronized input volley is, in Clarke's column and also in the dorsal column nuclei (3, 87), repetitive, and for the fact that some time is lost in relay, there is virtually nothing to signify that synaptic relay takes place in these nuclei. Naturally none of the foregoing proves absence of convergence; in fact, it might indicate the exact antithesis. The differences between certain motor and afferent relays nonetheless are worth pondering.

Local Sign in Reflex Action

There are in the nervous system many examples of what is called point-to-point localization (or projection). The relation of points in the occipital cortex to points in the retina, or points on the somatic sensory area to points on the body surface (4) come to mind in this connection. Something of this sort is seen in the myotatic reflex pathways and in these, serving as they do reflex actions narrowly limited to the zone of afferent origin, the localization is determined by anatomical limitation of connection (58, 67). However, local sign is preserved, in most circumstances, within a fraction of the synergic unit. Hence, and despite the fact that anatomical limitation of connection establishes the ultimate boundary of the field of action, a functional limitation of action to a fraction of that field is usual. Specifically an afferent nerve volley in the entire Group I supply to the gastrocnemius can involve the entire motoneuron pool of the gastrocnemius in monosynaptic reflex discharge. That no other motoneurons are discharged or excited subliminally (57, 58) implies anatomical limitation of monosynaptic reflex connection. In all ordinary circumstances a similar volley confined to the afferent fibers of the medial gastrocnemius will discharge only the medial gastrocnemius motoneurons (57), there being certain notable exceptions (1, 33, 41, 42, 64, 84). Action by the lateral gastrocnemius motoneurons is facilitated however (20, 57), which implies anatomical connection between them and medial gastrocnemius afferent fibers and hence limitation of the discharge zone by nature of connection rather than by absence of connection. In this instance the factor involved apparently is quantitative rather than qualitative (64).

A classical example of local sign, or reflex fractionation, is provided by flexion reflexes (16) which in all of their pathways involve internuncials (54). However set into action, the flexion reflex is not confined to a single flexor muscle nor to the synergist flexor muscles of a given joint but in varied intensity extends to the muscles of hip, knee and ankle. Table 1 exemplifies the argument. In it the tensions delivered by flexor muscles of the several joints are expressed as percentages of the strongest contraction, and the plurimuscular reflexes elicited by stimulation of each of three afferent nerves are represented. A study of table 1 will convince one that the limb left to itself would assume different final positions depending upon the afferent nerve stimulated.

From the foregoing one may infer something of the organization of the internuncial systems of the spinal cord, in this instance with specific reference to local sign. It seems quite certain that local sign in the flexion reflex mechanism cannot imply a 'private line' system as is, to a considerable extent, the case in monosynaptic systems.

TABLE 1. *Variation in Pattern of Reflex Flexion Involving Several Joints Depending upon the Nerve Stimulated**†

Afferent Nerve	Hip Flexor (Tens. Fasciae Fem.) %	Knee Flexor (Semitendinosus) %	Ankle Flexor (Tibialis Ant.) %
Internal saphenous	100	56	87
Popliteal (tibial)	3 or less	42	100
Peroneal (distal to ant. tibial n.)	14	100	69

* From Creed *et al.* (15); after Creed & Sherrington (16).

† In this table, the strength of contraction of the muscle responding most vigorously to stimulation of one afferent nerve is arbitrarily called 100 per cent. The contractions of the other muscles are expressed as percentages of that contracting most vigorously.

The internuncial mediate system of the flexion reflex clearly extends longitudinally to bind together the several motoneuron pools of the flexor muscles in a given limb. It is probable, could the system be activated uniformly, that the motor product would display a fixed pattern, which it manifestly does not in the circumstance of afferent stimulation. According to table 1, and the more complete original data of Creed & Sherrington (16), there is a tendency for the flexion reflex to be greatest when the segmental level of afferent inflow and motor outflow is in greatest approximation. This in general is true of the polysynaptic reflex discharges recordable in ventral roots on stimulation of various cutaneous nerves (54). Those cord potentials that signify internuncial activity (8) too are greatest at the level of afferent inflow. Considering these several evidences, the simplest conclusion would be that each longitudinal level of the internuncial system is engaged more or less in proportion to the density of impinging afferent collaterals and that the motoneurons in turn are proportionally driven by the interneurons.

After-Discharge

According to the general definition after-discharge is a discharge that continues after withdrawal of an external stimulus. With change of technique from the recording of muscle contraction to the recording

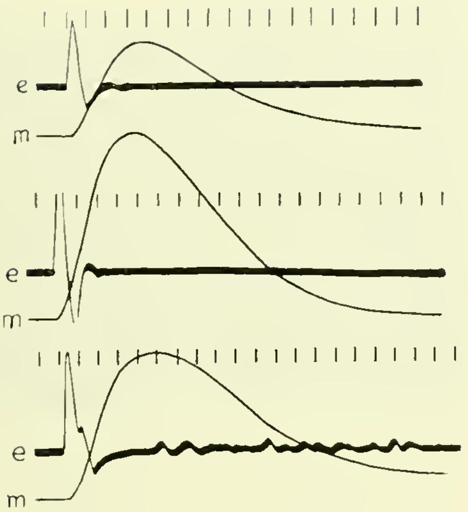


FIG. 8. Electrical (*e*) and mechanical (*m*) records of responses by the tibialis anterior muscle. Time, 10 msec. (*a*) Flexor reflex response to single shock stimulation of popliteal nerve at, presumably, Group II strength. (*b*) Maximal motor twitch elicited by a single break-shock to peroneal nerve. (*c*) Flexor reflex response obtained employing a strong stimulus (probably including Group III afferent fibers) to the popliteal nerve. [From Creed *et al.* (15).]

of motor nerve impulses this definition encountered difficulties. To exemplify: the 'single-shock' flexor reflex of figure 8*a* is essentially like the motor twitch recorded in figure 8*b*. One would not have said that the reflex displayed after-discharge and yet it is now known that the flexor reflex motor nerve impulses in just this situation are dispersed over 10 or more msec., greatly outlasting the external stimulus or the (virtually synchronous) afferent volley caused by it. The flexor reflex to stronger stimulation displayed in figure 8*c* would be said to show after-discharge. It is now known (88) that participation of Group III (delta) afferent fibers in the afferent volley is the condition for securing the reflex of figure 8*c*. After repetitive stimulation, contraction may continue for long periods. The fact has provoked much speculation as to the mechanism. Forbes (25) postulated 'long delay paths,' which is to say internuncial chains, as the mechanism, others an enduring state at the motoneuron. The best operational definition of after-discharge today would regard it as a discharge resulting from the arrival of presynaptic impulses but not immediately dependent upon the continued arrival of such impulses. So defined, after-discharge has been demonstrated in sympathetic ganglia (11) and may occur in the central nervous system.

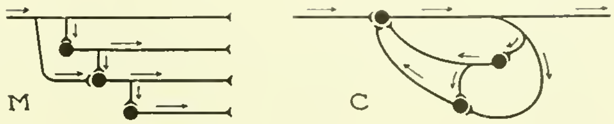


FIG. 9. Diagrams of the two fundamental patterns of internuncial circuits according to Lorente de Nó. *M*, multiple chain. *C*, closed chain. [From Lorente de Nó (71).]

Most of the delayed discharge encountered in the spinal cord can be traced to continued arrival at the motoneurons of internuncial impulses. The internuncial net then is a mechanism for temporal dispersion as well as spatial diffusion of action. The organization of interneurons to this end is next considered.

Multiple and Closed Internuncial Chains

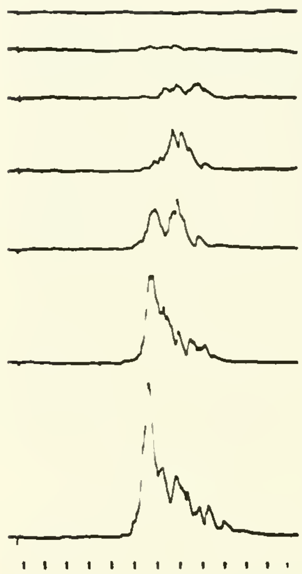
The internuncial systems are not only divergent and convergent in connection but also are linked in other manners made possible by the fact that they form chains of varying numbers of links. According to Lorente de Nó (70, 71) the infinitely complex internuncial paths of the central nervous system can be reduced, for sake of argument, to patterns, in repetition and combination, of two fundamental types of circuits—the multiple chain (*M* in fig. 9) and the closed chain (*C* in fig. 9). The closed chain is in essence the structure postulated by Forbes in his delay path hypothesis and by Ranson & Hinsey (82).

Temporal Characteristics of Action Through Internuncial Chains

Figure 10 illustrates the manner in which motoneurons respond under the influence of internuncial barrage set in action by stimulation of a cutaneous nerve at incrementing intensities (62). The behavior exemplified is that to be expected of a multiple chain type of internuncial organization [cf. Lorente de Nó (70, 71)]. Although the afferent input to the internuncial net is synchronous, the product of the internuncial action is dispersed over 6 or 7 msec. The subliminal influence exerted through the chain, which is evaluated by monosynaptic reflex tests of motoneuron excitability, begins earlier than and far outlasts the period of discharge. Thus it may be said that the paths of intermediate length in the chain are more powerful than those of lesser or

greater length. Figure 10 clearly shows another feature of chain activity; as input increases, the reflex progressively prefers the shorter paths. In a study of single motoneurons subjected to the same experimental conditions, Alvord & Fuortes (2) have shown that an individual motoneuron will respond with progressively diminishing latency and that it rarely responds more than once in the course of the internuncial bombardment, whatever may be the actual latency of the response it does yield. Thus there is clear proof that the paths of various lengths do in fact converge upon the individual motoneurons, as supposed in the diagram of figure 9*M*, and that increment in the early response may take place at the expense of later response by reason of refractoriness.

Reflex discharges, transmitted through internuncial chains, are frequently less simple than those recorded in figure 10. Employing the same afferent source, namely the sural nerve, or a comparable source, the course of excitability change in the motor nucleus (55, 59) and the motoneuron discharge resulting from internuncial activity display two or even three peaks (7, 54). Figure 11 illustrates the effect; it is from an experiment entirely comparable to that from which figure 10 was taken. It is seen that the two groups of discharges grow more or less in parallel with incrementing stimulation. The first peak of discharge compares with the total discharge in figure 10. Although there is no rigorous proof, it is generally considered that discharges of this character may indicate the operation, within the internuncial system, of closed chains. Recently an important and detailed study of the exact behavior of interneurons in a variety of circumstances has been commenced by Kolmodin & Skoglund (43) employing direct recording and a statistical approach. This eventually will provide a much needed direct picture of internuncial organization.



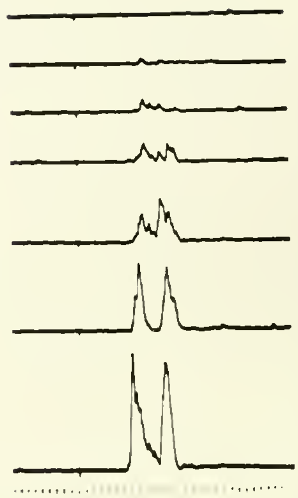


FIG. 10 (*left*). Flexor reflex discharges into the nerve of the semitendinosus elicited by single shocks of progressively incrementing strength to the sural nerve. Time, 1 msec. at bottom. [From Lloyd (62).]

FIG. 11 (*right*). Flexor reflex discharges elicited in nerve of semitendinosus by sural nerve stimulation with single shocks of incrementing strength. In this experiment the flexor reflex discharge occurs in two distinct peaks which grow with increasing stimulation in a more or less parallel manner. The first peak corresponds approximately to the entire discharge recorded in fig. 10. Note slower time base line. [From Lloyd (62).]

REFLEX ACTION OF MUSCULAR ORIGIN

Monosynaptic Myotatic Reflex

An important datum concerning the monosynaptic reflex elicited by stimulating the Group I afferent fibers of a given muscle nerve is that the reflex discharge returns to that nerve (fig. 12), which is to say to the muscle from which the afferent fibers concerned originate (54) and in all usual circumstances not to other nerves (64). In this the monosynaptic reflex has the quality of the myotatic reflex (52, 94) which fact led to the hypothesis that the monosynaptic connections within the spinal cord indeed are the mechanism for transmission of the stretch reflex (54, 55). Confirmation of the hypothesis required proof that the reflex elicited by natural stimulus, that is by stretch, is in fact monosynaptic, proof of which is seen in figure 13. Another important correlation is that the monosynaptic reflex elicited by nerve stimulation just like the natural myotatic reflex (52, 94) does not display after-discharge.

The monosynaptic reflex as evoked by single-shock nerve stimulation resembles closely the 'tendon jerk' which is a fractional manifestation of the myotatic reflex (52), the phasic component, in effect, rather than the static component. In a static, or maintained, stretch response, which is seen to best advantage in the extensor muscle of the decerebrate preparation, other factors come into operation, although the mechanism proper is purely spinal (18). Impulses descending from supraspinal levels support the reaction and the small motor fiber system plays upon the muscle spindles to control the afferent response therefrom (32, 44, 45, 51). It is important

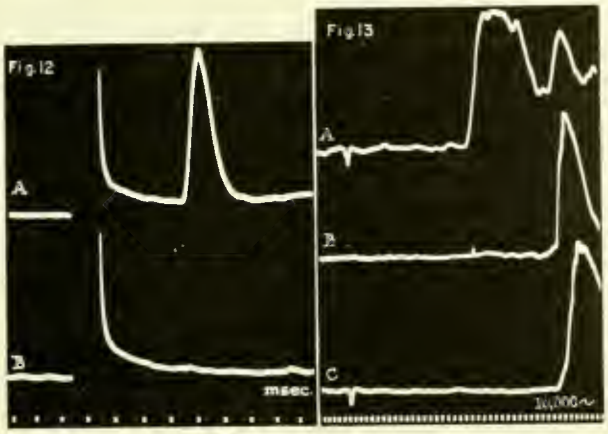


FIG. 12. Monosynaptic reflex response obtained by a single shock stimulation of, and by recording from, the tibial nerve. Following break in the recording there is seen in *A* the tail of the action potential conducted directly from stimulating to recording leads and, approximately 4 msec. later, the monosynaptic reflex volley. In *B* the reflex volley is lost following severance of appropriate dorsal roots. [From Lloyd (59).]

FIG. 13. Proof of stretch origin of monosynaptic reflex. *A*. Afferent response evoked by stretch of gastrocnemius and recorded from the first sacral dorsal root at a given point. *B*. Segmental monosynaptic reflex evoked by stimulation at that same point on the dorsal root and recorded from the first sacral ventral root at a given point. *C*. Reflex response evoked by stretch of gastrocnemius recorded from that point on the ventral root. The sum of the latencies in *A* and *B* approximates that in *C*, hence response *C* is monosynaptic. [From Lloyd (59).]

to realize that the natural reflex operates under closed circuit conditions permitting 'feedback' (32), whereas the monosynaptic reflex is usually observed under open loop conditions.

Many studies have been made of tendon jerk and myotatic reflex latency (cf. 52, 55) and its brevity has been conceded generally. It was often thought of as monosynaptic; and indeed on a basis of latency, the tendon jerk was even thought to be an idiomuscular reaction dependent only upon muscle tone which was in turn dependent upon intact reflex connections. Not until exact measurements of synaptic delay (71) and of conduction time were available was it possible to prove the exact manner of central connection.

Monosynaptic Reflex Relations Between Synergists

As has been noted, the field of action of a monosynaptic reflex is limited by anatomical limitation of monosynaptic connection established by any given afferent fiber source. As a generality, there is no monosynaptic excitatory connection between muscles that act upon different joints. Thus quadriceps and gastrocnemius, or biceps and tibialis anterior, are without monosynaptic reflex interconnection (50). There is, however, between two muscles or two fractions, or heads, of a muscle that act in concert upon a given joint, established monosynaptic reflex connection. In usual circumstances monosynaptic reflex afferent impulses from one muscle or head of such a pair facilitate action by the motoneurons of the other (cf. fig. 14) but do not discharge those motoneurons. The difference between homonymous connections (those between the afferent fibers and motoneurons of a single muscle) that transmit readily and heteronymous connections (those between synergists) that do not transmit readily are essentially quantitative (64, 68) and appear to result from differences in number and aggregation of individual active synaptic contacts (knobs) (38).

Heteronymous monosynaptic reflex transmission will take place to a small degree in several experimental circumstances: during the period of increased response following a high frequency stimulation called posttetanic potentiation (fig. 15), during repetitive stimulation at frequencies between approximately 60 and 150 or more per sec. (1), if a high degree of 'background activity' is present as in well-developed decerebrate rigidity (1) or in long spinal reflex action (67, 68), and in the chilled preparation (64).

The muscles bound together by excitatory monosynaptic connection in common action at a joint constitute a synergic unit; thus the parts of the triceps surae (soleus, medial and lateral gastrocnemius) form such a unit as do the biceps femoris posterior and semitendinosus (fig. 14).

Monosynaptic Reflex Relations Between Antagonists

Monosynaptic reflex action of afferent fibers upon motoneurons is not limited to excitation. There are inhibitory connections (57, 58) and, as in the case of excitation, the field of inhibitory monosynaptic action is limited by anatomical limitation of connection. The monosynaptic reflex afferent fibers from a muscle of a given joint inhibit action by the motoneurons of its direct antagonist at that joint but not of those acting at other joints (fig. 16). Thus the tibialis anterior and triceps, flexor and extensor of the ankle, respectively, are linked by inhibitory interconnection as are the quadriceps and biceps of the knee, whereas the muscles of the ankle and of the knee are independent in inhibitory monosynaptic action as in excitatory.

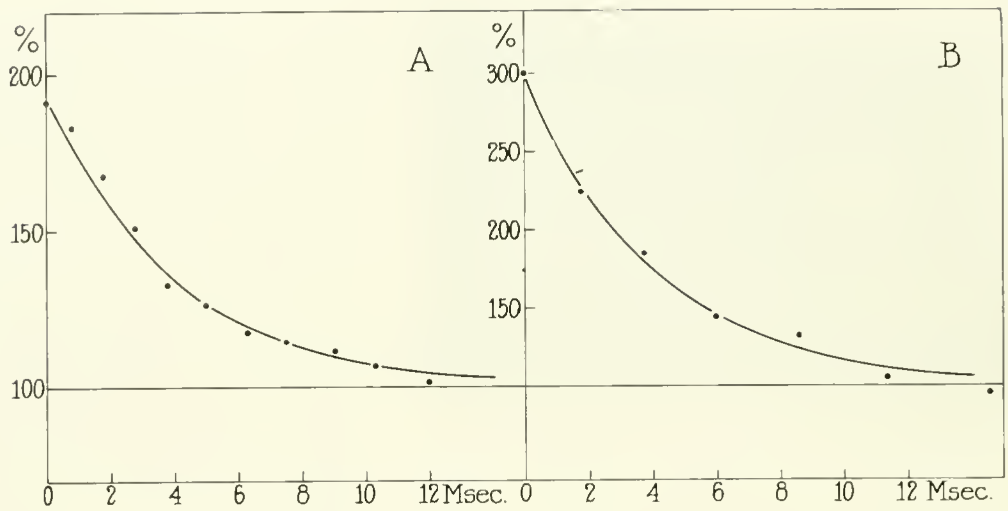


FIG. 14. *A*. Monosynaptic reflex facilitation of monosynaptic reflexes pertaining to one head of gastrocnemius by Group I afferent volleys engendered in the nerve to the other head. *B*. Monosynaptic reflex facilitation of monosynaptic reflex of biceps femoris posterior by Group I afferent volleys from its synergist, semitendinosus. [From Lloyd (59).]

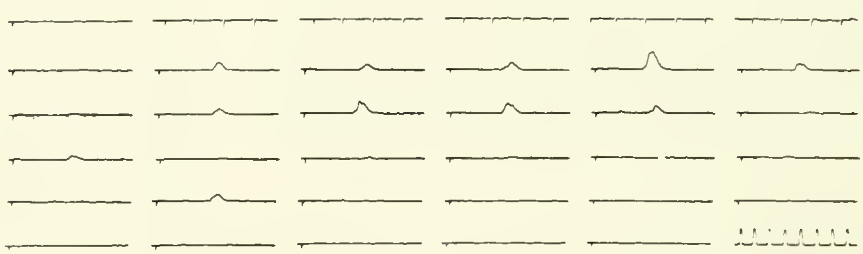
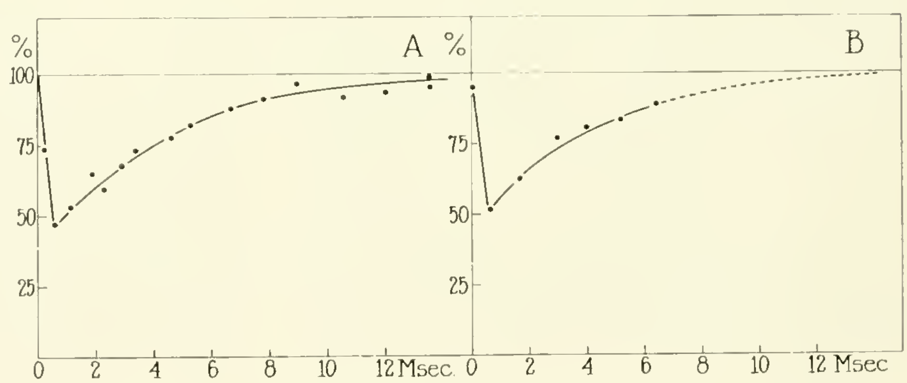


FIG. 15. Heteronymous monosynaptic reflex transmission occurring in small amount in the period following a high frequency stimulation of the afferent nerve. Afferent pathway from medial gastrocnemius stimulated, recording from the motor nerve to the lateral gastrocnemius. Recordings, reading from *left to right* and *from above downward*, were made each 2 sec. before, during a 10-sec. tetanus at 500 per sec. (stimulus artifacts seen in the *second to sixth records* of the *top row*) and after tetanization. *Last record*, at *bottom right*, is time in msec. [From Lloyd *et al.* (64).]

FIG. 16. *A*. Monosynaptic reflex inhibition of the tibialis anterior monosynaptic reflexes by Group I afferent volleys from the triceps surae. *B*. Monosynaptic reflex inhibition of the triceps surae by Group I afferent volleys from the deep peroneal nerve (representing ankle flexors and digital dorsiflexor). [From Lloyd (59).]



Concept of Myotatic Unit

The outstanding feature of the myotatic reflex pathways, excitatory and inhibitory[1], is that the afferent fibers connect directly with the motoneurons. The functional meaning of this fact is that the motoneurons inevitably are influenced whenever the muscle spindles generate impulses in the Group IA afferent fibers arising within them. In this the myotatic reflex differs seemingly from all others. One can see readily that individual muscles could be isolated from influence of all other sorts by inhibition of the internuncial links interposed between the afferent influx and the motoneuron. They cannot be isolated from the self-engendered postural influence. Reflex standing (94) involves the play of a number of stretch reflexes so that the entire limb is held in the face of gravity. But if, for purpose of argument, one were to conceive of gravity acting upon but a single muscle, say the medial gastrocnemius, the influence would indeed be felt by the motoneurons of that muscle, but also action by the lateral gastrocnemius and soleus would be facilitated and by the tibialis anterior and extensor longus, the antagonists, would be depressed. Other muscles would remain uninfluenced. Let the gravity play upon the tibialis anterior alone and the situation would be reversed. The muscles at a given joint are mutually dependent at the myotatic level of postural performance in the sense that none can be influenced independently of the others. Such a group of mutually dependent muscles together with the monosynaptic reflex connections that bind them constitute a myotatic unit (58).

Lengthening Reaction or Inverse Myotatic Reflex

If weak conditioning volleys in the nerve to one fraction of a synergic unit are employed in conjunction with testing monosynaptic reflexes engendered by stimulating the nerve to the remainder of the synergic unit, simple facilitation curves of the sort illustrated in figure 14 usually can be obtained (20, 35, 50, 57, 58). On strengthening the conditioning volleys, the action still being confined to Group I afferent fibers, a sudden break in the direction of inhibition occurs, as exemplified by the difference between curves *A* and *B* to the left of figure 17. A latency differential of approximately 0.6 msec. between facilitatory and inhibitory action bespeaks the existence of an internuncial relay in the inhibitory path. It may be noted that inclusion of the Group II fibers in the conditioning activity brings forth the further change with still longer latency [characteristic for Group II action (cf. fig. 19)] indicated by curve *C*. Initial divergence from the simple facilitation is always inhibitory. The further change denoted by curve *C* is inhibitory in an extensor nucleus but facilitatory in a flexor nucleus.

The Group I inhibitory action in a synergic unit is due to action by the Group IB fibers and has all the proper attributes for designation as an expression of the lengthening reaction. It is concluded that this reaction is mediated through a disynaptic reflex pathway. In line with these results and conclusion Granit (31) has shown that large afferent fibers are concerned with autogenic inhibition (i.e. inhibition within the synergic unit), and McCouch *et al.* (75) have observed inhibition of the quadriceps by electrical stimulation of the crureus tendon wherein would lie Golgi tendon organs.

Associated with the lengthening reaction is an excitation of antagonists. To the right of figure 17 one sees in curve *A* the simple inhibition of an antagonist due to Group IA action. In curve *B* the course of that inhibitory action is interrupted by an excitatory action that is the precise counterpart of Group IB inhibition within the synergic unit. To complete the experimental series, curve *C* illustrates the additional inhibitory influence of including the conditioning action of the Group II fibers.

The lengthening reaction thus appears to be but one aspect of action of a reflex mechanism that is precisely opposed to that of the myotatic reflex mechanism and differing from it in central organization only in the matter of possessing an internuncial relay. For this reason the over-all reaction is appropriately termed the inverse myotatic reflex.

A disynaptic inhibitory connection exists between certain muscles that are not co-members of a myotatic unit (fig. 18). For this no associated excitatory action has been found. The function of these connections is not understood, although their existence accounts for the inhibition of certain muscles concomitant with elicitation of a tendon jerk in others, a phenomenon described by Denny-Brown (17).

Stretch Flexor Reflex

Stimulation of muscular afferent fibers in the Group II and Group III bands produces effects in the pattern of the flexor reflex. Because of Hunt's study (37) of

[1] The notion that monosynaptic inhibitory pathways are monosynaptic is not universally conceded at the present time (22). This question is discussed in another connection.

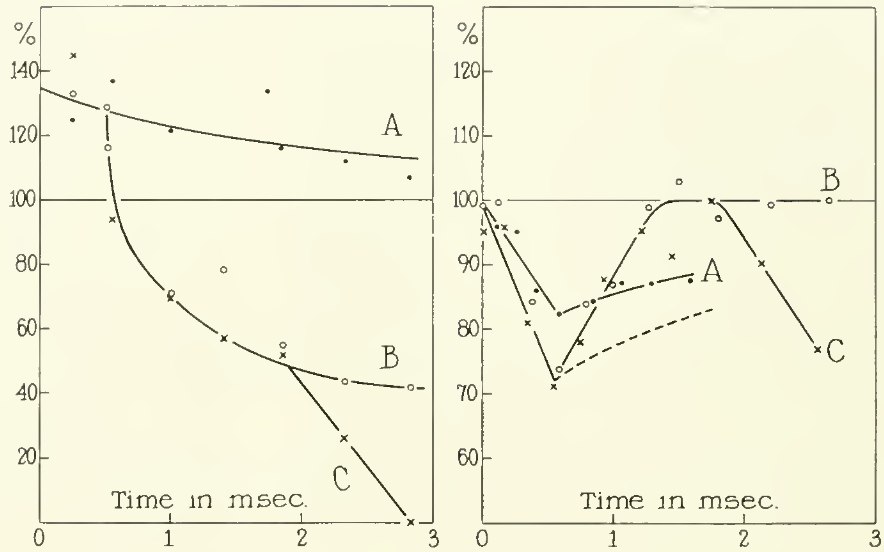


FIG. 17. To illustrate Group I B disynaptic inhibition of synergists and facilitation of antagonists. *Left. Curve A*, simple facilitation of plantaris monosynaptic reflexes by weak Group I afferent volleys in the afferent fibers of its synergist, the flexor longus digitorum. *Curve B*, the conditioning volleys having been strengthened, but still confined to Group I fibers, an inhibitory action supervenes with an added latency of approximately 0.6 msec., indicating the presence of an interneuron in the inhibitory pathway. *Curve C*, further conditioning effect caused by adding Group II fibers to the afferent conditioning input. *Right. Curve A*, simple monosynaptic reflex inhibition of plantaris monosynaptic reflexes by weak Group I afferent volleys from its antagonist, the extensor longus digitorum. *Curve C*, further conditioning effect caused by addition of Group II fiber activity to the conditioning volleys. *Ordinates:* test reflex amplitude in per cent of control value set at 100. *Abscissae:* time in msec., zero time indicating coincidence of Group I conditioning and testing afferent volleys. [Rearranged from Laporte & Lloyd (50).]

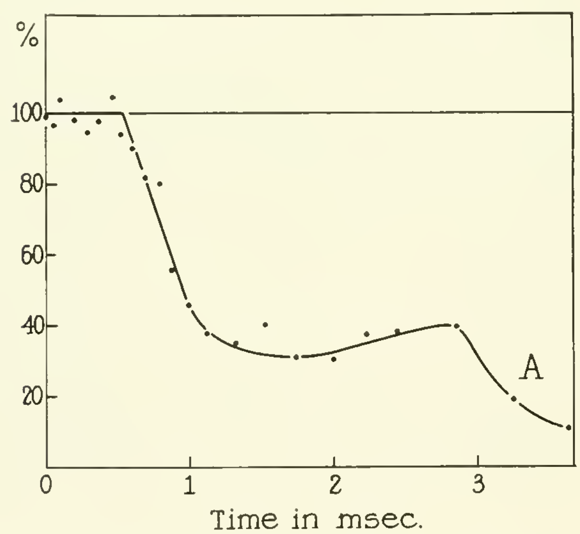


FIG. 18. Disynaptic reflex inhibition between muscles that are not partners in a myotatic unit. Inhibition of monosynaptic reflexes of triceps surae by afferent volleys in the nerve of flexor longus digitorum. The initial phase of depression is due to Group I fibers acting through an interneuron, the second phase to Group II fibers. [After Laporte & Lloyd (50).]

the afferent fibers from muscle discussed in connection with figure 2, it is known that the entire Group II band arises in the secondary, or flower-spray, endings of the muscle spindle. Thus there is every reason to suppose that the action they engender represents the stretch flexor reflex.

In the experimental situation the flexor reflex action of Group II muscle afferent fibers is not powerful and frequently does not secure an overt reflex discharge (cf. fig. 21*F*). It is easily disclosed, however, by utilizing suitable monosynaptic reflexes as tests for influence upon the motoneurons. To obtain the Group II reflex effect uncontaminated by Group I reflexes, the muscle of origin for the Group II afferent volleys and the muscle of origin for the test monosynaptic reflex must not be partners in a myotatic unit. In figure 19 are to be found examples of the Group II action, excitatory in a flexor nucleus, inhibitory in an extensor nucleus. The latency for onset of effect, approximately 2 msec., is in part concerned with differential conduction time (the Group II conditioning volleys travel at lower velocity than the Group I testing

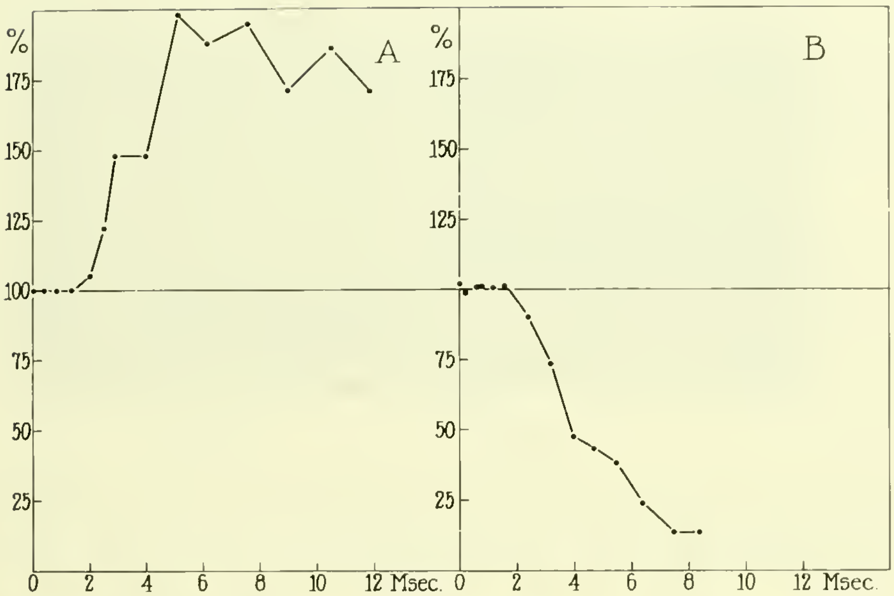


FIG. 19. Conditioning of flexor and extensor motoneurons by Group II afferent volleys. *A.* Facilitation of knee-flexor monosynaptic reflexes by afferent volleys from the deep peroneal nerve. *B.* Inhibition of flexor longus (a physiological extensor) monosynaptic reflexes by afferent volleys from tibialis posterior. In neither instance does Group I, monosynaptic or disynaptic, reflex conditioning occur. [From Lloyd (59).]

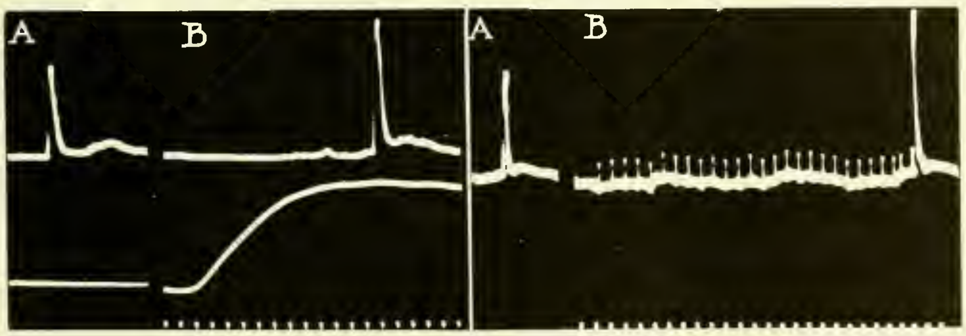


FIG. 20. *Left.* Effect of stretch-evoked afferent discharge from the gastrocnemius upon the flexor hamstring monosynaptic reflex response. *Upper records* contain the reflex responses; *lower records* measure the tension in the gastrocnemius. *A.* Control reflex response. *B.* Facilitated reflex response during stretch which is signalled by rise in the lower record. Time, 1 msec. *Right.* Effect upon flexor hamstring monosynaptic reflex test of gastrocnemius muscle spindle afferent activity provoked by tetanic stimulation of 20 isolated fusimotor fibers (small motor fibers or gamma efferents) supplying intrafusal muscle fibers of the gastrocnemius. *A.* Control response. *B.* Facilitated response, the small deflections indicating stimuli to fusimotor fibers. Time, 2 msec. [Unpublished records kindly provided by Hunt (cf. 36).]

volleys) but for the most part with central delay occasioned by the presence of interneurons in the pathway.

An important step in establishing the secondary endings of muscle spindles, and the Group II fibers afferent from spindles, as the origin of a true stretch flexor reflex is to show that natural stimulation, as by stretch or contraction of the intrafusal muscle fibers, can lead to a flexor reflex result (36). Figure 20 on the left shows that mild stretch of the gastrocnemius facilitates a monosynaptic reflex of the flexor hamstrings, and on the right shows the same result on contraction of intrafusal muscle fibers in gastrocnemius. It is, of course, essential that the conditioning and test muscles be selected for known absence of Group I reflex interconnection since the means employed for natural stimulation are adequate also for activation of the Group I fibers.

In parallel with excitation of flexors inhibition of extensors takes place; in short, the total pattern of a flexor reflex is thrown into action. This is true whether

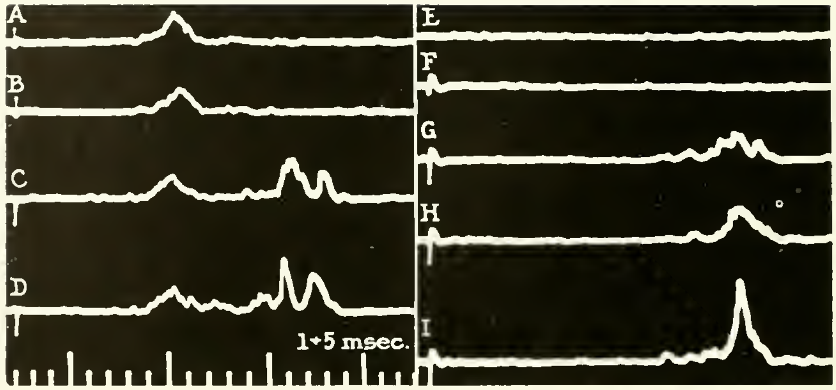


FIG. 21. Flexor reflex discharges provoked by stimulation of Group II and Group III afferent fibers in cutaneous and muscle nerves. *A, B.* Stimulation of the sural (cutaneous) nerve at Group II strength. *C, D.* Stimulation of the sural nerve at Group III strength. *E.* Blank sweep. *F.* Stimulation of the gastrocnemius nerve at Group II strength which, in this experiment, secured no reflex discharge. *G, H, I.* Stimulation of the gastrocnemius nerve at Group III strength. All recordings from the peroneal nerve which supplies the pretibial flexors and dorsiflexors of the digits. [From Lloyd (54).]

the source of Group II activity aroused by natural stimulation be a flexor or an extensor muscle. Furthermore, the degree of stretch necessary to provoke action of this system is so small as not conceivably to be painful. Hence the Group II flexor reflex or muscular origin seems indeed to be concerned with reflex regulation of posture and movement rather than reaction to painful stimulation.

Group III Flexor Reflexes

Stimulation of Group III muscle afferent fibers provokes a flexor reflex (54), an example of which is seen in figure 21 *G, H, I.* The precise function of these fibers has not been established (37), but it is a reasonable assumption that they are nociceptive, in which case the Group III flexor reflexes would be true nociceptive withdrawal reflexes.

REFLEX ACTION OF CUTANEOUS ORIGIN

According to inspection (95) and myographic analysis the dominant reflex pattern elicitable by stimulation of the skin, or of cutaneous nerves, is one of ipsilateral flexion and contralateral extension (30). Exceptions to the rule exist (19, 26, 89) and there are in observation of the dominant reflexes evidences of the existence of concealed reflexes (15, 96).

Low and High Threshold Flexor Reflexes

Fibers in both the Group II band (i.e. alpha and beta fibers) and the Group III band (i.e. delta fibers) on stimulation give a flexor reflex result in the ipsilateral limb (fig. 21, *A–D*). The minimum anatomical pathway for these reflexes contains one internuncial relay. The two sorts of flexor reflex differ somewhat in character. Presence or absence of after-discharge, as was noted briefly in connection with figure 8, was found by Tureen (88) to depend upon whether or not the delta (i.e. Group III) fibers were stimulated. In a more recent study, Brooks & Fuortes (13) have confirmed the difference between the response to 'weak' and 'strong' stimulation with respect to after-discharge. Although they did not identify the afferent fibers concerned, their weak stimulation may be presumed to have stimulated Group II and their strong stimulation to have embraced Group III (fig. 22). Their belief that the entire Group II reflex might be monosynaptic was not substantiated by the later study of Alvord & Fuortes (2), which latter is in agreement with the generality that flexor reflexes are polysynaptic. Brooks & Fuortes made the important observation that the 'weak' stimulus in single shock circumstances did not bring about an organized withdrawal of the limb whereas the 'strong' stimulus did. The former, yielding "an inconspicuous twitch" is considered to express "a very simple and unorganized reflex property of the spinal cord . . . while the after-

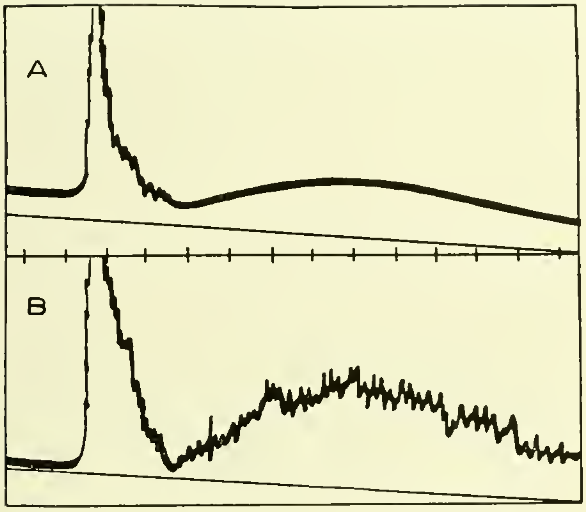


FIG. 22. Ventral root potentials resulting from single shock stimulation of an ipsilateral cutaneous nerve. The recording leads were arranged so that electrotonic potentials extending into the root from central structures as well as impulse discharges were recorded. *A*. Weak stimulus (possibly of Group II) not followed by after-discharge. *B*. Stronger stimulus (possibly of Group III) resulting in withdrawal of the limb and marked after-discharge. [From Brooks & Fuortes (13).]

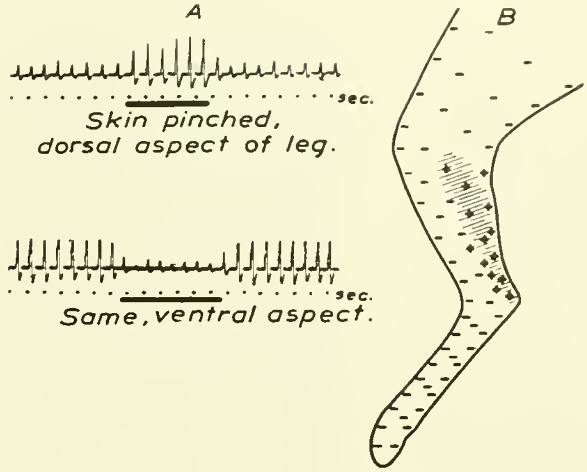


FIG. 23. Conditioning influence upon monosynaptic reflex of the gastrocnemius, an ankle extensor, of 'pinch' stimuli applied to various points on the skin of the hind limb. The *upper record* in *A* shows enhancement of rhythmically elicited monosynaptic reflexes when the crosshatched area, as represented in *B*, was stimulated. The *lower record* in *A* shows inhibition when other areas of the limb were stimulated. In *B*, + and − indicate areas facilitating and inhibiting the extensor test reflex. [From Hagbarth (34).]

discharge is the correlate of elaborated reflex activity capable of giving rise to organized and purposeful movements." This concept is not very clear, the more so because Tureen's (88) repetitive stimulation at Group II strength produced a better maintained contraction (without after-discharge) than did the stronger stimulation which revealed evidence of 'concealed inhibition' followed by after-discharge. Because natural reflexes would surely be evoked by repetitive activity one cannot agree that the Group II flexor reflex pathways would not represent a mechanism for organized purposive reflex action.

Because there is no positive information concerning the upper limit in diameter of 'pain' fibers (28), one cannot state dogmatically that the Group II reflex is not a nociceptive reflex; but it seems improbable. The Group III reflex, on the contrary, cannot incontestibly be considered a nociceptive reaction; but 'pain' fibers are concentrated in this group and in the C fiber group, so that the likelihood in this instance is great.

Special Effects From Specific Regions

Many exceptions to the rule of ipsilateral flexion exist (26, 34, 91, 96) either as responses of extension or in the form of concealed reflexes. The extensor thrust (89) is a well-known example. It is elicited by pressure between the toe pads. The afferent fibers for this reflex are restricted to the plantar nerves (89), but stimulation of the plantar nerves themselves induces a flexor reflex despite the necessary presence within them of fibers that cause ipsilateral extension.

A systematic basis for some of the mixed effects elicitable by stimulation of cutaneous nerves has been put forward recently by Hagbarth (34) who utilized monosynaptic reflexes of various muscles as test systems and conditioned these with action initiated not by electrical stimulation but by pinching the skin at various loci. Such stimulation applied over most of the limb facilitated the flexor monosynaptic test reflexes and inhibited the extensor tests. However, a flexor monosynaptic reflex test was inhibited rather than facilitated if a skin area over its antagonist was stimulated, and an extensor test was facilitated rather than inhibited when the skin overlying the extensor itself was stimulated. This latter observation is exemplified in figure 23. The rule then is that the skin area over a given antagonist pair, unlike the remainder of the skin of the limb, is for that pair re-

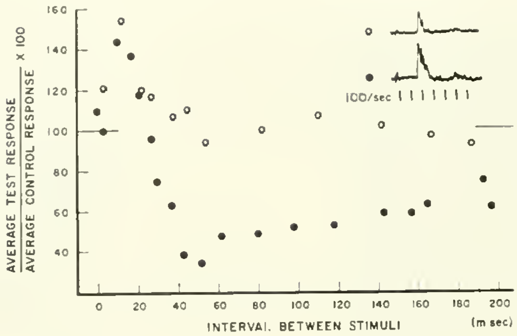


FIG. 24. Crossed conditioning of flexor reflexes by Group II and Group III afferent fibers. Test reflex recorded from the semitendinosus and elicited by stimulation of the peroneal nerve. Contralateral conditioning by volleys in the tibial nerve at two strengths. These conditioning volleys produced ipsilaterally the reflexes shown in the *inset*. *Hollow circles*, crossed conditioning of flexor reflex by the weaker volleys; *solid circles*, by the stronger volleys. The essential distinction is the powerful crossed inhibition of the flexor motoneurons by Group III afferent fiber action. [From Perl (78).]

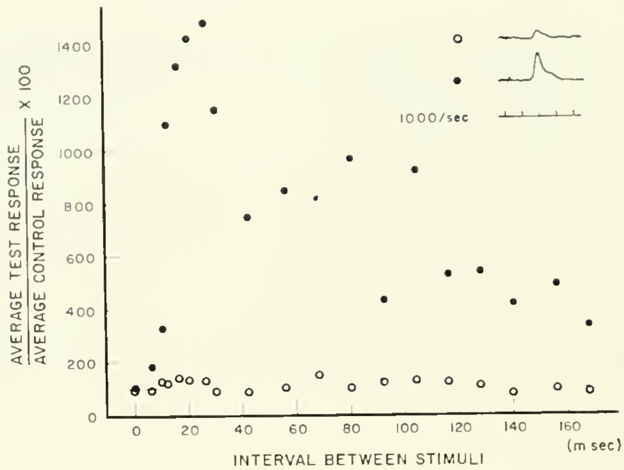


FIG. 25. Crossed conditioning of quadriceps monosynaptic reflexes by afferent volleys of two strengths applied to the saphenous nerve. *Inset* shows monitor records of the conditioning afferent activity. *Hollow circles*, effect of the weaker crossed saphenous afferent volleys. *Solid circles*, strong facilitation of the extensor motoneurons by the action of crossed saphenous Group III fibers. [From Perl (78).]

ceptive for an ipsilateral extensor reflex rather than a flexor reflex.

Crossed Reflexes of Cutaneous Origin

The classical crossed reaction of the decerebrate preparation is the so-called crossed extensor reflex. Immediately after spinal section the overt contralateral response is flexion which is after a period of time replaced by extension (76). There are, therefore, crossed excitatory connections to both flexor and extensor motor nuclei, although with change of state one end result may predominate. The nature of these connections, at least as they are thrown into action from cutaneous sources, has been clarified to some extent by Perl (78).

When Group II afferent fibers are stimulated, the action of crossed knee and ankle flexor motoneurons is facilitated (fig. 24, open circles) and discharge occurs occasionally. If the Group III fibers be active as well, there is no significant change in flexor facilitation; but a prolonged period of inhibition follows (fig. 24, filled circles).

In an extensor nucleus little effect, and that in the direction of inhibition, is encountered as a consequence of stimulating contralateral Group II fibers (fig. 25, open circles). Once Group III fibers are stimulated there is an enduring facilitation (fig. 25, filled circles) of the crossed extensor motoneurons which is fully comparable to the inhibition of crossed flexors caused by similar stimulations.

If now one considers these contralateral effects together with the ipsilateral effects discussed earlier, it is seen that Group II afferent fibers of cutaneous origin in action set in motion a bilateral flexor reflex. What may be its functional role is not clear, largely it may be said because the receptor origin is not clear. Nevertheless, the machinery for this bilateral flexor response is present and the response itself probably is not a nociceptive reaction. On the contrary, origin and nature of the Group III response, flexion ipsilaterally, extension contralaterally, is sufficiently elaborated as to leave little doubt that Group III afferent fibers are responsible for the classical reflex couplet of the nociceptive flexor reflex and the reflex of crossed extension (30).

Reflex Effects of Unmyelinated Afferent Fibers

Reflex function of the unmyelinated, or C fibers, was first demonstrated unequivocally by Clark *et al.* (14) who described respiratory and arterial pressure changes consequent to stimulation of them.

In the cat, Laporte & Boër have encountered in ventral roots of the lumbar enlargement a prolonged reflex discharge due to the stimulation of C fibers (49). In a more complete study of 'C fiber reflexes' in batrachians, Laporte (46) and Laporte & Boër (48) have shown that the reflex discharge is directed into flexor muscles and that ipsilateral extensors are in-

hibited; they conclude from this that the reflex action represented is nociceptive. Pain being heavily represented in the C fiber bands in mammals (28), it is a fair assumption that the reflex in mammals too is nociceptive in nature.

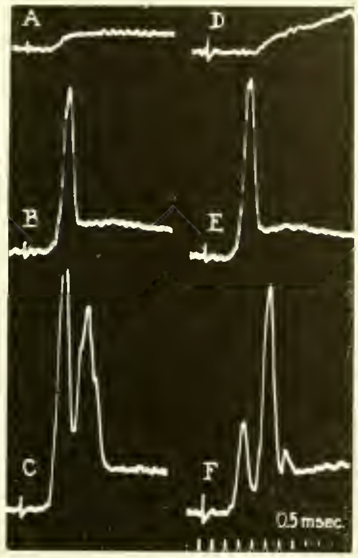


FIG. 26. Ipsilateral and contralateral postsynaptic potentials and reflex discharges in the third sacral segment. Complete description in text. [From Wilson & Lloyd (98).]

SPINAL ORGANIZATION FOR REFLEX CONTROL OF MIDLINE STRUCTURES

Most of that which is known of spinal reflex organization has to do with those regions innervating the limbs. At the caudal end of the spinal cord, specifically the last sacral and caudal segments, reflex control is concerned with mid-line structures conspicuous among which, in the cat, is the tail. The terminal segments of the spinal cord have a structure differing from that characteristic of the enlargements (81), the principle distinguishing features being the presence of a large dorsal mid-line nucleus, or 'broadening of the dorsal gray commissure' (83) and the decussation of primary afferent fibers (97).

The terminal segments display special organization from a functional point of view to match the structural specialization (98). Some aspects of this are illustrated in figures 26 and 27. Records *A*, *B* and *C* of figure 26 show the ipsilateral result, recorded on the third sacral ventral root, of stimulating the third sacral dorsal root. At the weakest strength *A* a monosynaptic postsynaptic potential is recorded. Stronger stimulation, still at Group I strength, brings out a monosynaptic reflex discharge *B*. Still stronger stimulation evokes, in addition to the monosynaptic reflex which in this experiment is further augmented, a prominent disynaptic reflex *C* which is nearly as synchronous in character as is the monosynaptic reflex. Only at this last strength of stimulation does any change occur in consequence of stimulating the contralateral root. It consists of a postsynaptic potential of latency 0.8 to 1.0 msec. longer than that recorded following ipsilateral stimulation *D*, from which fact a disynaptic pathway is postulated. Conjoint stimulation of contralateral dorsal root at the strength employed for record *D* and of ipsilateral dorsal root at a strength that evokes a monosynaptic reflex record *E*, the stimuli being synchronous, produces the result recorded in record *F*. The monosynaptic reflex usually is inhibited, and by a disynaptic convergence a large disynaptic reflex is realized. There is, therefore, a convergence upon the motoneurons of ipsilateral excitatory and contralateral inhibitory connections from Group I primary afferent fibers. Also there is an internuncial nucleus that receives excitatory connections from primary afferent fibers of both sides and which in turn relays to the motoneurons. There is as yet no information as to the location of this internuncial nucleus, but it is not unlikely that the dorsal mid-line nucleus, peculiar to the region, is responsible for the powerful bilateral disynaptic relay which likewise is peculiar to the region.

The third sacral segment provides a unique system for determining unequivocally the nature of the direct inhibitory pathway between primary afferent fibers and motoneurons. This type of connection was originally described (53, 57) as being monosynaptic, a view that has been attacked vigorously (22) and the presence of an 'inhibitory interneuron' postulated in order to simplify the nature of a chemical hypothesis of excitation and inhibition. Conclusion as to the presence or absence of this postulated interneuron depends upon interpretation of the time relations between conditioning inhibitory activity and testing excitatory activity, or upon latencies for production in motoneurons of excitatory and inhibitory postsynaptic potentials. It is evident that most of the systems for study of inhibitory action in monosynaptic reflexes are not satisfactory, with uncertainties as to longitudinal conduction in the cord and, indeed, as to what to measure being difficulties. The bilateral system of the third sacral segment obviates all these difficulties for one can dispense with all questions of conduction in the pathways to the motoneurons. To achieve this, it is necessary only to observe the monosynaptic reflexes of both sides simultaneously and to vary the relation between the afferent volleys in such

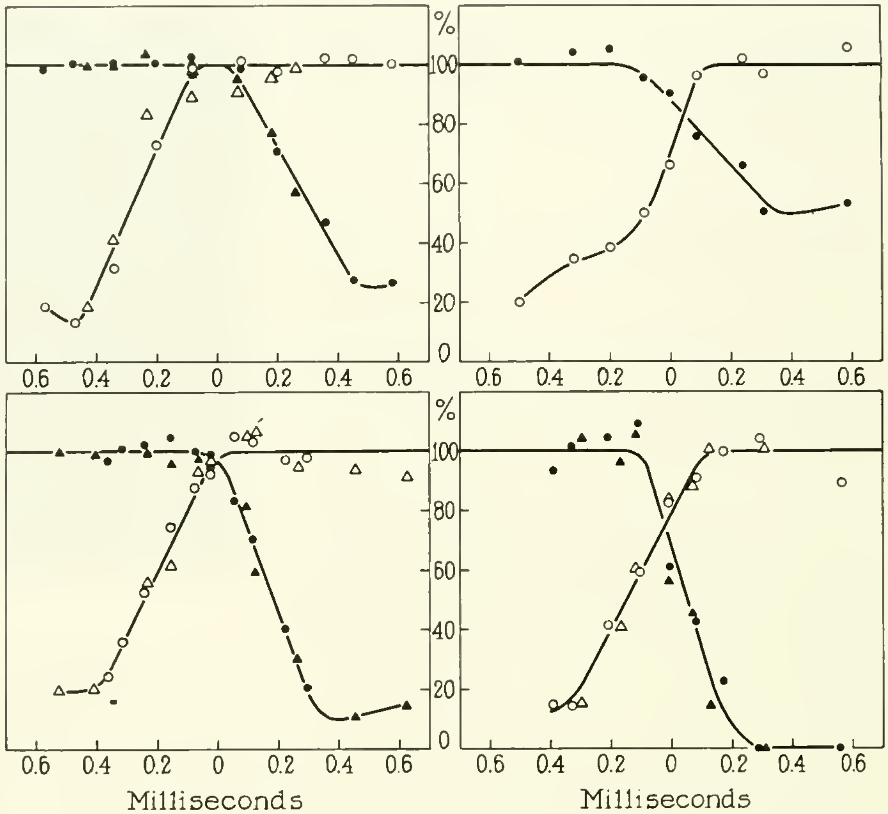


FIG. 27. Simultaneous conditioning effects upon the monosynaptic reflexes of the two sides of the third sacral segment caused by the Group I afferent volleys employed to elicit those reflexes. *Open symbols*, mean amplitude of monosynaptic reflexes on one side. *Closed symbols*, mean amplitude of monosynaptic reflexes on the other side. *Triangles* and *circles* represent independently made observations by the two authors. Further description in text. [From Wilson & Lloyd (98).]

a way that one of them initially antecedes, then coincides with and finally trails the other. Figure 27 illustrates the result of four such experiments. If the latency for inhibition were longer than that for excitation, which it is conceded would necessarily be the case if the inhibitory path contained an interneuron in series, there would be a period on either side of synchrony during which neither reflex would be inhibited. Making every possible allowance, that period would amount to a minimum of 0.2 to 0.3 msec. on either side of synchrony. From the results in figure 27 the only possible conclusion is that the inhibitory pathway, like the excitatory pathway, is monosynaptic. It is evident, therefore, that the chemical hypothesis in its present form is not adequate to accomodate the facts.

Unfortunately the exact peripheral origin of the afferent fibers concerned in the monosynaptic and disynaptic pathways of the lower sacral and caudal segments is not known. The monosynaptic pathways presumably serve for reciprocal innervation of the lateral tail muscles.

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CHAPTER XXXVII

Central autonomic mechanisms[1]

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CHAPTER CONTENTS

INTRODUCTION

THE JACKSONIAN CONCEPT OF LEVELS of central nervous functions has been a very useful one because it has the appearance of simplicity, which is illusory, and furnishes a logical basis for exposition. The central organization of autonomic function is but little different from the somatic in this regard. Thus segmental patterns exist in the spinal cord and also, so far as cranial nerves are concerned, extend into the brain stem. Reflex arcs for autonomic activity are developed at all these segmental levels, and a certain amount of local integration of function is possible. However, for the greatest benefit of the organism as a whole these segmental activities must be amalgamated, adjusted and regulated so that the body is maintained in the best possible condition to respond to the necessities imposed by the often changing environment. Thus, suprasegmental mechanisms have developed in the brain stem, the hypothalamus, the cerebellum possibly and the cerebral hemisphere. Here again we see some evidence of levels, for the medullary 'centers' are concerned with relatively fundamental things, such as the regulation of cardiac activity, vasomotor control and respiration. In the hypothalamus we also have forms of organization which influence these basic functions, but also much more complicated circuits are set up which may be concerned with certain types of behavior, with the consumption of food and with the various types of general responses to environmental changes which bear sharply upon the individual. The cerebral mechanisms for autonomic function have developed along with its somatic functions to a considerable extent, as Sherrington pointed out, along with increased use of distance receptor mechanisms and with the need for developing total patterns of behavior which are the best suited for the needs of the biological type in question. The neopallial and archipallial portions of the hemisphere interact with the hypothalamus and even lower regions in the brain stem, not only to affect autonomic functions but also to bring these functions into the behavioral structure.

[1] The results of some recent experiments by the author and his colleagues are briefly touched upon in this paper. This work was supported by USPHS grant M 375 (C3).

The autonomic manifestations of an emotion are exceedingly important since they may enable the individual to live with that emotion as well as to support and maintain it. The relationships of an individual with his environment and with his fellow beings are based upon a proper emotional orientation and suitable modulation of autonomic activity.

It would be impossible to discuss autonomic activities alone. These are so commingled with somatic as to require a comprehensive viewpoint. Both autonomic and somatic reflex outflows may be evoked by common somatic or visceral inputs, and central autonomic centers may control or modulate both autonomic and somatic peripheral activities.

SPINAL AUTONOMIC MECHANISMS

Certain autonomic functions proceed in mammals which have been experimentally deprived of higher regulatory influences. These functions are relatively simple, for there is no doubt that loss of connections with the brain eliminates or greatly modifies the more complex sorts of autonomic activities. However, study of these remaining activities in animals which have been subjected to decapitation or section of the spinal cord have confirmed that the basic functional organization of the autonomic portion of the nervous system, as for the somatic, lies in its reflex arcs. The organization of these arcs varies greatly, from simple monosynaptic connections between visceral afferent and visceral efferent neurons to very complex mechanisms involving many intermediary neurons as well as the primary afferent and efferent ones. When sufficient numbers of such units which subserve a common type of response are grouped at a certain level of the nervous system such groupings are customarily referred to as 'centers.' Certainly this term has been of considerable value in the physiologist's notation, but as the complexities and vagaries of neural organization have revealed themselves, it hardly seems proper to hold to such a simple concept (74).

Nevertheless, groupings of efferent neurons devoted to specific autonomic responses do occur in the spinal cord, and from these the notion of spinal autonomic centers is derived. These have a fairly uniform segmental arrangement, similar to somatic reflex patterns, and correspond roughly to the segments of outflow. The visceral afferent neurons, the cell bodies of which lie in the dorsal root ganglia, are arranged similarly to the somatic afferents and their peripheral distribution shows evidence of segmentation, allowing for developmentally induced displacements of the deep viscera. It is no longer held that afferent neurons are present in autonomic ganglia, although a few aberrant ones may at times be found elsewhere in the nerve roots and trunks.

Anatomical Considerations

An historical survey of the development of knowledge of the autonomic outflow is not properly a part of this chapter; such surveys have been written by Sheehan (151, 152), Mitchell (121) and Gaskell (59). However, recognition of the division into thoracic and sacral outflows contributed much to the knowledge of central autonomic mechanisms. Workers prior to 1885 were handicapped by Bichat's concept of animalic (concerned with somatic) and organic (concerned with nutritional regulation) systems which implied an independence of the sympathetic nervous system in spite of the fact that the rami communicantes have been known for many years. A number of histological and developmental studies culminated in Gaskell's work of 1886 (58) in which, as a result of anatomical and physiological observations, he recognized that the white rami communicantes were restricted in the dog to the thoracic and upper lumbar regions. Gaskell studied the fiber composition of the white rami and traced fine myelinated fibers from the ventral roots through these rami into the sympathetic chain. The association between these fibers and the unmyelinated fibers emerging from the ganglia was recognized on physiological grounds, since cardiac acceleration could be produced by stimulation of either. Gaskell found similar fibers in the central roots of the second and third sacral nerves and discerned that these connected with collateral ganglia of the pelvis rather than with the chain ganglia. None of these preganglionic fibers was found in the cervical nerve roots. Thus the concept of thoracicolumbar and sacral divisions was born. Similar preganglionic fibers were found and traced in certain cranial nerves, beginning with the spinal portion of the accessory nerve. Further experimental work by Gaskell and his co-workers and by others established the details of structural and functional differences between the craniosacral and thoracicolumbar divisions of the autonomic system. Nearly all of this has been more recently confirmed. Sheehan (152) has examined the spinal autonomic outflows in man and found that, if any cervical contribution to the thoracicolumbar system exists, it must be very rare indeed. The human sacral outflow is usually from S3 and S4, with occasional small contributions from S2 or S5.

Our particular interest here lies in the central sta-

tions of these outflows, the location of the cell bodies of the neurons giving rise to the preganglionic fibers, and of so-called internuncial neurons which may participate in visceral reflex circuits. Gaskell in 1885 noted that the distribution of neurons in the 'lateral horn' (intermediolateral gray column) corresponded closely with the distribution of the thoracicolumbar sympathetic fibers, and he suggested that the cells of this group gave rise to these fibers. It is interesting incidentally that Gaskell did not approve the terms preganglionic and postganglionic. It was his view that the neurons we are accustomed to call postganglionic (after Langley) were simply shifted from their original position during development, retaining their functions and relationships as 'effector' or 'motor' elements, in other phraseology, forming the lower motor neurons of the sympathetic system. The neurons of the intermediolateral gray column, then, according to Gaskell, are 'connector' neurons presumably homologous with similar neurons which may be intercalated between pyramidal tract fibers and the anterior horn somatic motor neurons. There are certain merits in this proposal.

The preganglionic spinal neurons are smaller than the somatic efferent cells and are also multipolar, with finer and more scattered chromidia which are especially concentrated at the periphery of the perikaryon. The chromidial pattern is quite variable and makes the determination of chromatolytic or other pathological changes difficult and often undependable. According to Mitchell (121) cells of this type have been found elsewhere in the cord than in the intermediolateral column, and an intermediomedial column has been described. However, in man there is said to be no definite column in the medial part of the pars intermedia but simply scattered cells of this type. Although some of these cells may simply be intercalated neurons devoted to other functions, it would not be surprising if there were some variable scatter from the lateral column. Mitchell also makes a point of mentioning that autonomic type neurons have been described in the dorsolateral portions of the anterior gray columns in the cervical region and stresses the proximity of these neurons to the spinal accessory roots. Small myelinated fibers from the latter have been traced into the vagus nerve; and while these may perhaps be sympathetic, the possibility that the neurons mentioned may be displaced cranial parasympathetic elements has not been considered. It is also possible that they are related to the nucleus ambiguus and concerned with control of certain striated muscles of the neck.

Spinal Autonomic Reflexes

It is generally held that spinal autonomic reflex arcs may be monosynaptic or multisynaptic (26, 27). The latter types make provision for delayed responses and enduring reactions in which there is considerable after-discharge. They also must provide for mediation of certain types of suprasegmental control, including facilitation and inhibition, much as in somatic reflexes as indicated by Eccles (49). The anatomical identity and specific connections of these internuncial neuron pools are not well-known, although there must be provision for such mechanisms as reverberating circuits.

The organization of these reflex neuronal pools is primarily segmental, not necessarily in the sense of single segments but involving certain groups of segments, as is shown in the following list for thoracicolumbar reflexes [modified from Kuntz (99)].

Head and neck	T1–5
Upper extremity	T2–9
Lacrimal gland (sympathetic)	T1–3
Vasomotor responses, piloerection and sweating	
upper trunk	T4–9
lower trunk	T9–L2
lower extremities	T12–L2
Pupillodilatation	C8–T1 (2)
Cardiac acceleration	T2–6
Abdominal viscera	T4–L2
Genitourinary and rectoanal (sympathetic) responses	L1–L2

It is obvious that these may vary considerably. There may also be interactions among these reflexes as well as mass discharges involving many of them. It is commonly held that mass discharge is a characteristic of the thoracicolumbar system, while more specific effects are produced by the craniosacral division. This usually loosely stated view is related to the relatively long-lasting effects of the chemical effector substances produced by the orthosympathetic elements. However, while it is in general true, one must make some reservations even as did Cannon (37) who, although he stressed the diffuse discharge idea, said, "The sympathetico-adrenal system though organized for diffuse and widespread action may influence excessively separate organs or functions." More specifically, recent experiments have shown that autonomic discharges may be largely segmental (61). Thus, stimulation of the spinal cord in animals at T4 produces a marked rise in arterial pressure without pupillary dilatation. On stimulation from T3 to T1, the pupil response appears and increases while the

pressor response disappears. Selective retraction of the nictitating membrane may also be elicited. Such selective effects may also be obtained from autonomic areas in the brain where these differences are perhaps due to the differences in neuronal thresholds and distribution. In the cord, however, production of specific autonomic discharges depends upon segmental arrangement. When a mass discharge takes place, as in emotion, it is probably associated with activation of large areas of higher autonomic mechanisms. An excellent tabulation of the autonomic innervation of the most important structures together with their central nervous representation is to be found in Mitchell (121).

It seems obvious that reflex mechanisms in the spinal cord are so organized that a variety of reflex patterns may be set up. Thus there are pure visceral reflexes, for example, changes in arterial pressure after mechanical (or other) stimulation of viscera such as the intestine, pancreas, etc. Such reflexes are best studied in spinal animals; otherwise investigators have found themselves involved in semiphilosophical considerations of the specificity of visceral pain, as did Lewis & Kelgren (102) and von Euler & Sjöstrand (163). There are also reflex patterns which serve both visceral and somatic functions. Thus we have somatovisceral reflexes, such as the vasomotor response to stimulation of a 'somatic' nerve. There are viscerosomatic ('visceromotor') reflexes, in which contraction of somatic musculature occurs in response to stimulation of visceral afferent fibers, for instance contraction of abdominal muscles upon irritation of abdominal viscera or peritoneum.

The mass of work done on the vasomotor activities of sympathetic nerves after the original observations of Bernard (23–25) and Brown-Sequard (36) culminated in Bayliss' summary of the vasomotor system (19), which every student of neurophysiology and neuroanatomy should read as an exercise in classical physiology. Segmentally arranged spinal vasomotor reflex arcs are present in the cord and are capable of activity even when cut off from the brain, as shown by stimulation of peripheral somatic and splanchnic nerves with resulting increase in arterial pressure and peripheral vasoconstriction. These responses are diminished during spinal shock but are very easily obtained after recovery from this state. These spinal reflex mechanisms have been held to be excited by asphyxia (154) or perhaps by chemical changes brought about by anoxia. They are less sensitive to increases in carbon dioxide than are the medullary centers. Bayliss points out that it is difficult to determine whether the chemical changes themselves stimulate efferent vasoconstrictor impulses or whether reflex stimulation is also necessary. The existence of vasodilator reflex mechanisms at the spinal level is not as certain, but Bayliss felt that they do exist in cases where local vasodilator responses can be induced. The extent to which spinal vasomotor reflexes function in either the intact or spinal animal is uncertain.

Other spinal reflex mechanisms may also be affected by chemical changes in the body fluids. Thus, in spinal cats in which hypoglycemia was induced by insulin in doses equivalent to those which produce strong sympathicoadrenal activation in normal animals, there was also activation of this system and therewith resistance to the hypoglycemia (35). Since this occurred when all nervous connections between the brain and the thoracicolumbar outflow were severed, spinal mechanisms which are capable of activating the sympathicoadrenal system exist. It is also possible that changes in blood temperature may affect thermoregulatory reflexes, such as those involved in sweating and vasomotor changes. Thus, cooling of one extremity may bring about vasoconstriction in the opposite one according to Sahs & Fulton (144). Certain local sudomotor responses may occur in response to visceral irritation, and local sweating has been described especially in areas of skin contact in spinal and sympathectomized persons. Such local responses may well be due to axon reflexes (174).

Viscerosomatic reflexes were studied in amphibians and reptiles by Carlson & Luckhardt (38) in 1921; limb movements in response to visceral stimulation were observed. Miller and his co-workers (116–119) extended such observations to decapitate mammals, noting contractions of abdominal and hind limb muscles upon mechanical stimulation of abdominal viscera and electrical stimulation of the splanchnic nerves. Downman & MacSwiney (48) found similar responses as well as increases in arterial pressure upon pinching the intestine and mesentery in cats with spinal cord transection in the upper thoracic region.

Subsequently Downman (46, 47) carried out a more detailed analysis of the central organization of viscerosomatic reflex arcs, using decerebrate and spinal cats and comparing such arcs with those involved in somatic reflexes. In the first instance the greater splanchnic nerve was stimulated with single shocks; in the second a nearby intercostal nerve was used. The efferent discharges were recorded from intercostal and lumbar nerves. The reflex discharge elicited by splanchnic stimulation in spinal cats was of relatively long duration due to repetitive firing of

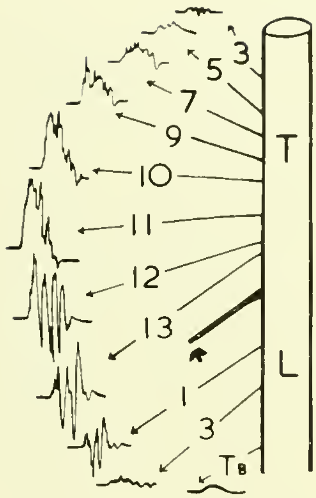

FIG. 1. Viscerosomatic reflexes. Maximal single-shock stimulation of splanchnic nerve evokes reflex volleys in body wall nerves, shown as they were recorded off the central crushed end of each nerve. Volleys recorded consecutively. *T 3 to 13*, intercostal nerves; *L 1 to 3*, lumbar nerves. Acute spinal cat, cord transected at T1. [From Downman (47).]

motor neurons. There was considerable irradiation from the splanchnic input into all intercostal and lumbar nerves and even into leg nerves. The recorded motor volleys were largest in the lower thoracic and upper lumbar nerves, a situation seemingly adapted to the abdominal splinting which occurs with irritation of the abdominal viscera (fig. 1). It is of interest that excitation from splanchnic stimulation spreads much faster than does that from intercostal stimulation, the velocity of spread being three to five times greater in the former (20 to 50 m per sec. compared with 7 to 11 m per sec.). Two routes for splanchnic irradiation are involved—a fast extraspinal path in the sympathetic chain of the same side and a slower intraspinal route of limited extent. Intercostal reflexes can use only the latter type of pathway. Contralateral spread is entirely intraspinal. This visceromotor reflex discharge may be so extensive that in animals with high cervical spinal transection, strong splanchnic stimulation evoked diaphragmatic contraction. The efferent splanchnic fibers involved are apparently in the small A group, the A gamma-delta size.

Interrelations with Higher Levels

Viscerosomatic reflex discharges are greater and more widely spread in the spinal than in the decerebrate preparation. Severing the spinal cord seems to release the spinal arcs from some inhibiting influence which affects the viscerosomatic reflex pathways more than the somatic ones. Another difference between decerebrate and spinal preparations is the fact that, following an initial conditioning reflex discharge, a later testing discharge into the same nerve of outflow shows facilitation in the former and inhibition in the latter.

Downman also measured in spinal cats the central delays for reflex discharges evoked by stimulation of the splanchnic and of the intercostal nerve. The average delays ranged from 5 to 8.1 msec. in the case of the viscerosomatic and from 2.4 to 2.8 msec. for the somatic arcs, which indicates that a greater number of neurons is involved in the splanchnic arcs. The extent of this internuncial activity apparently is less in decerebrate than in spinal animals which may account for the differences in effect of conditioning afferent stimulation.

Downman also points out that there are at least three ascending paths available for impulses of splanchnic origin—an extraspinal one by way of the sympathetic chain which eventually enters the spinal cord, an ipsilateral route in the fasciculus gracilis and slower conducting bilateral paths in the anterolateral region of the white matter. Besides setting up visceral reflex arcs at various levels of the cord, such pathways also extend to the brain where suprasegmental control mechanisms may be brought into play with feedback to the reflex center. Some of these paths reach the cerebral cortex, and Amassian (4) found that such impulses are conveyed by A beta fibers which lie in the posterior funiculus between the afferent fibers from the upper and lower extremities. There are also A gamma-delta groups of fibers of splanchnic origin which can affect cortical activity. Amassian believes that such afferent paths may take origin in the mesenteries and visceral Pacinian corpuscles, accounting for sensory awareness of as well as responses to visceral distention. Aidar *et al.* (2) found that afferent impulses of splanchnic origin ascend at least as high as the thalamus, the faster impulses passing via fibers in the ipsilateral posterior funiculus and the opposite medial lemniscus (possibly mediating pressure and tension), while the slower traverse the lateral spinothalamic tracts bilaterally (possibly mediating pain). It is of special interest that some slow impulses reach the posterior part of the hypothalamus.

The importance of suprasegmental connections for visceral mechanisms in the spinal cord is attested by the release phenomena exhibited in the spinal animal

as well as the deterioration of such protective functions as temperature and blood glucose homeostasis. The routes of these connections are then of interest, although our information is at best sketchy. It has been suggested by Gillilan (62) that the so-called reticulospinal tracts of Papez (129) are concerned with autonomic activity. These include *a*) the lateral reticulospinal tract, located in the medial part of the lateral funiculus and said to be concerned with thermoregulatory sweating on the face; *b*) the ventral reticulospinal tract which lies in the ventral funiculus and is concerned with vascular control and sweating of the body and extremities; *c*) the ventrolateral reticulospinal tract in the ventrolateral part of the lateral funiculus which participates in regulation of respiration, being connected with the motor neurons of the respiratory muscles and having origin, it is said, in the respiratory areas of the brain stem; *d*) the medial reticulospinal tract in the anterior funiculus which is said to descend from various autonomic areas of the brain stem and may help integrate parasympathetic and sympathetic activities. The location of descending sympathetic fibers in the anterolateral white matter of the spinal cord was noted by Sherrington (153) in 1887; this localization has been reaffirmed clinically many times more recently by chordotomy for relief of pain. Experimentally in animals there is good evidence for such a location for descending fibers mediating pressor and bladder responses (171). The pressor pathways undergo partial decussation in the brain stem and are multisynaptic above the spinal cord, at least. There are also decussations below the cervical cord level, both for pathways from the hypothalamus and from the medulla oblongata; some backcrossing is also present in the spinal cord according to Harrison *et al.* (71). Thus, stimulation of sympathetic areas on the right side of the brain stem may produce effects on the same side even after hemisection of the cord in the cervical region. Descending pathways for bladder contraction have decussations in the brain stem and lower lumbar segments in animals but have no cross connections in the remainder of the cord. Pathways for respiratory control lie in the anterior and anterolateral portions of the white matter in cats (135). Pressor responses of cerebral cortical origin are also mediated by bilateral pathways in the anterolateral region (95). In general, these localizations seem also to apply in man, since Foerster (52, 53) found evidence in his patients of bilateral pathways for vasoconstriction and sweating in this anterolateral region.

When these rich paths for the modulation of autonomic activity in the spinal cord are severed, certain basic patterns are retained and remain functional at a reflex, automatic level. We have noted that vasomotor and viscerosomatic reflexes may remain active. It is well-known that the mechanisms for defecation and micturition may regain adequate levels of reflex function and may be subject to a degree of control by imposed cutaneous stimulation. The neural patterns for sexual function remain and can operate without the influence of the brain, provided the proper hormonal milieu is present. In animals, these patterns include appropriate somatic attitudes. Temperature adjustments remain poor. In this homeostatic function the diencephalon is pre-eminent.

Spinal Shock

The phenomena of acute spinal shock are especially striking in so-called higher echelons of the vertebrate group. In lower forms reflex activity may proceed without delay after severance of the spinal cord, but in primates there is a lull in the functioning of the isolated cord which in the past has posed problems to the clinician. In general, autonomic functions are less affected than somatic, although the onset of automaticity of bladder and bowel functions may be considerably delayed, even in carnivores. The cause of spinal shock cannot be stated precisely, although Sherrington hypothesized a possible 'isolation dystrophy' affecting neurons of the spinal cord after separation from higher mechanisms. Certainly the cord neurons, normally adapted to powerful extraneous influences, excitatory and inhibitory, which are probably chemical, must undergo a dramatic change in reactivity when these influences are cut off. In lower forms these influences seem chiefly reticulospinal and vestibulospinal (57); in man, however, the corticospinal connections seem more important. Since visceral mechanisms are perhaps ordinarily less modulated by impulses from the brain than are the somatic, these readapt with greater facility than the latter. However, some of the great homeostatic complexes, temperature regulation for instance, cannot reassume function when the brain connections are severed.

Influence of Distance Receptors

Sherrington considered the great influences of the brain upon both autonomic and voluntary activities to be dependent upon the development of the distance receptors 'the great inaugurators of reaction.'

"By a high spinal transection the splendid motor machinery of the vertebrate is practically as a whole and at one stroke severed from all the universe except its own microcosm and an environmental film some millimeters thick immediately next its body. The deeper depression of reaction into which the higher animal as contrasted with the lower sinks when made spinal signifies that in the higher types more than in the lower the great distance-receptors actuate the motor organ and impel the actions of the individual. The deeper depression shows that as the individual ascends the scale of being the more reactive does it become as an individual to the circumnambient universe outside itself. It is significant that spinal shock hardly at all affects the nervous reactions of the interoceptors (visceral system); and that it does not affect the intero-ceptive arcs appreciably more in the monkey than in the frog. . . . Not that in the highest animal forms the 'distance-receptor' merely *per se* has necessarily reached more perfection or more competence than in the lower. . . . It is that in the higher types there is based upon the 'distance-receptors' a relatively enormous neural superstructure possessing million-sided connections with multitudinous other arcs and representing untold potentialities for redistribution of so-to-say stored stimuli by *associative recall*. The development and elaboration of this internal nervous mechanism attached to the organs of distance-reception has, so far as we can judge, far outstripped progressive elaboration of the peripheral receptive organs themselves. Adaptation and improvement would seem to have been more precious assets in the former than in the latter" (154).

Of these adaptive phenomena at both spinal and cerebral levels we are, perhaps, acquiring some glimmerings. Of the 'enormous neural superstructure' we have more records of detailed observations on neopallial, rhinencephalic, diencephalic and bulbar mechanisms than were available to Sherrington, but one wonders if we have deeper insight.

AUTONOMIC MECHANISMS OF SUBDIENCEPHALIC BRAIN STEM

Reticular Formation

It is axiomatic that progressive encephalization in the nervous system has produced increasing anatomical complexity as one proceeds from one level to another. Thus through the brain stem we have extensive ascending and descending pathways for interrelating the functions of the higher regions and the spinal cord. Collaterals from these pathways connect with organized nuclear groups of neurons, cell stations for cranial nerves, bundles of fibers concerned with modulation of these various functions, and many other integrated systems. These known masses of fibers and neurons are embedded in a matrix of incredible complexity, which in recent years has attracted increasing attention as the 'reticular formation of the brain stem.' Segundo (150) has recently summarized briefly the knowledge of the structure of the reticular formation and cites Ramón y Cajal's conclusions as to the constitution of the dense interstitial plexus which forms this reticulum. Thus we have fibers coming from the spinal cord; from the medial lemniscus which is constituted of sensory fibers of the second order and which contributes collaterals to reticular cells; motor pathways, including collaterals from the pyramidal tract; fibers from interstitial motor cells; and fibers from the cerebellum, acoustic nuclei, and the colliculi of the midbrain. A careful investigation of the structure of this area, which extends from the lower part of the bulb into the diencephalon, has been initiated by Scheibel & Scheibel (148) who have found collaterals from the main ascending and descending tracts passing into the reticular formation and setting up complex axodendritic-somatic synapses which seem to make possible a potential interaction between dendritic and somatic neuronal fields. The axons of the reticular formation have very large potential areas of interaction with other neurons, theoretically with as many as 27,000 others, although of course the number undoubtedly is much less in many cases. The axons of the reticular formation neurons and those axons passing through the reticular formation have widespread connections, with many collaterals and bifurcations (fig. 2). The reticular formation has connections with the hypothalamus, the subthalamus and thalamus, and possibly even with the cortex. Besides the ascending systems there is evidence that the descending systems are just as complex.

Medulla Oblongata and Pons

In this maze are embedded the groups of neurons which are known to be related to efferent outflow through the cranial nerves and through the spinal cord. It seems unnecessary to review the structure and location of these entities as they are well described in various textbooks of neuroanatomy and in such monographs as that of Mitchell (122). While these nuclear groups have definite and known functions

FIG. 2. Reconstruction of single neurons in the reticular formation, showing the extensive ramifications of cell processes. The axons send major branches toward the cerebrum and also caudally into the spinal cord. [Figure by A. Scheibel and M. Scheibel, from French (55).]

and serve as the final common pathways for these important autonomic activities, it is not appropriate to designate any of them as the so-called 'centers of vital activity' of the brain stem, since 'centers' may greatly transcend any restricted locality. Nevertheless in the lower part of the brain stem, in such a small area as the medulla, we have a fairly compact grouping of the neural arrangements which make possible integration of some very important vital regulations.

CIRCULATORY REGULATION. According to Mitchell, the functions of the medulla oblongata in regulation of the heart first became known about 1845, and in 1873 Dittmar (45) showed that if the brain stem is gradually sliced away from above downwards, a fall in arterial pressure is observed after transection in the middle of the pons. Progressive transections then cause greater and greater falls until the upper part of the medulla is reached. These findings were held to indicate that a center for arterial pressure regulation, perhaps controlling vasoconstriction, was located in the upper part of the medulla. No further progress was made until 1916 when Ranson & Billingsley (138) showed that both pressor and depressor responses could be elicited by stimulation of the floor of the fourth ventricle in cats. Stimulation in the posterior part of the fourth ventricle just lateral to the obex beneath the area postrema produced decreases in arterial pressure. Stimulation in the inferior fovea at the apex of the ala cinerea gave increases in pressure (fig. 3). Ranson's observations were extended, among others, by Alexander (3) in 1946, who found by the method of stereotaxic exploration that a pressor center occupies an extensive region in the lateral reticular formation and the rostral two thirds of the medulla, while the depressor center includes a greater part of the medial reticular formation in the caudal half of the medulla. This center was shown to be functionally significant because of its capacity for tonic inhibition of the spinal cardiovascular mechanisms. The necessity of these structures for the occurrence of cardiovascular responses produced by stimulating somatic

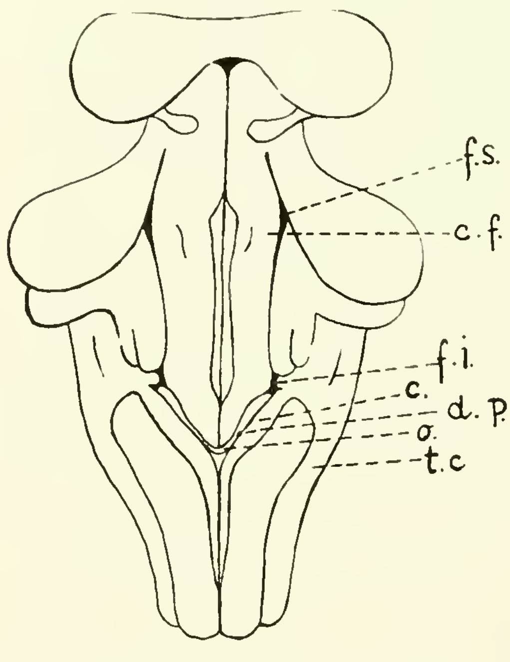

FIG. 3. Pressor and depressor areas of the floor of the fourth ventricle of the cat. *F.i.*, fovea inferior, site of the pressor area; *d.p.*, depressor point; *f.s.*, fovea superior; *c.f.*, facial colliculus; *c.*, clava; *o.*, obex; *t.c.*, tuberculum cinereum. [From Ranson & Billingsley (138).]

nerves was also shown. The afferent and efferent paths for the various circulatory reflexes are presented in detail by Uvnäs in Chapter XLIV of this volume.

CONTROL OF RESPIRATION AND ALLIED FUNCTIONS. In 1916 Miller & Sherrington (115) also explored the floor of the fourth ventricle with electrical stimulation in decerebrate cats and found that stimulation of a very restricted area of the inferior fovea produced swallowing (fig. 4). There was concurrent arrest of respiratory movements and also increased pulse rate. These phenomena were also shown to occur in normal swallowing. In other early experiments Graham Brown (65) stimulated the surface of the transected brain stem of a chimpanzee and from the region of the central gray obtained an increased respiratory rate and a sound which resembled laughter. It remained for Pitts and his collaborators, however, to explore thoroughly the respiratory mechanisms of the lower brain stem (136). The medullary respiratory center has been found to have two parts bilaterally located. The first, for inspiration, is located in the ventral reticular formation immediately overlying the rostral four fifths of the inferior olive and extending a few millimeters to each side of the mid-line. Increase in the carbon dioxide content of body fluids causes increase in the frequency of discharge and recruitment of neurons in this center and, as a consequence, increase of the depth of inspiration. The center for expiration is located in the dorsal reticular formation, dorsal and slightly rostral to and cupped over the end of the inspiratory area. It acts, in part at least, by inhibiting the inspiratory center. Upon these centrally located mechanisms varying types of afferent impulses converge from the skin, the nose, the bronchi, the lungs, etc. Chemical changes in the blood and accumulation of metabolites affect the cells of these centers directly; they also stimulate peripheral chemoreceptors which send afferent impulses into the respiratory mechanisms. Since nervous control of respiration will be thoroughly discussed in Chapter XLIII of this volume by Oberholzer & Tofani, a detailed discussion is not in order here. Briefly, the regulation of rhythmic respiration appears to depend upon the alternating activity of the two portions of the respiratory center. This activity depends upon several factors, of which one is a vagal reflex system sensitive to stretch of the lungs; another

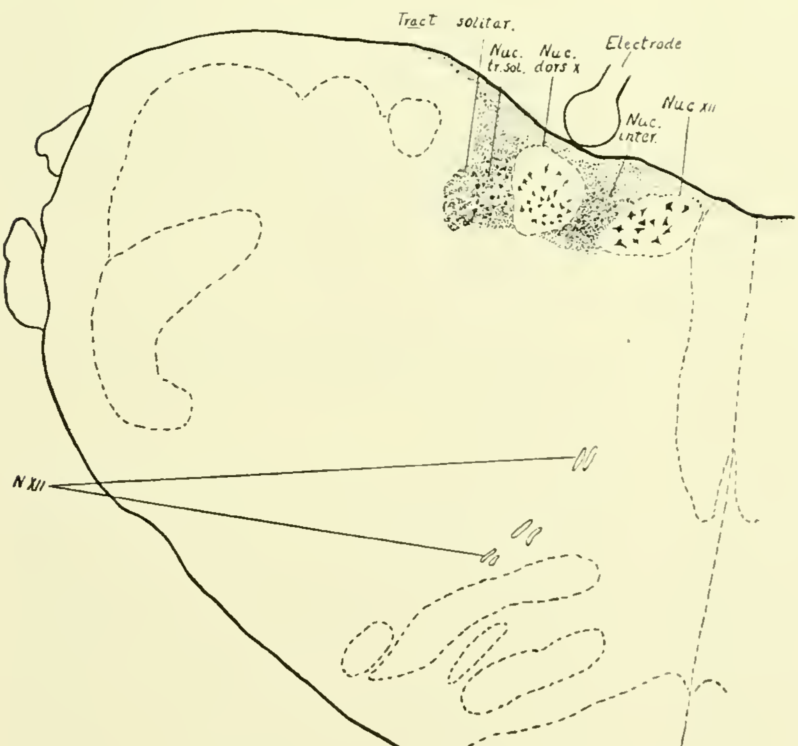

FIG. 4. Cardiac and respiratory changes associated with swallowing induced by stimulation of the floor of the fourth ventricle in the decerebrate cat. The point of application of the stigmatic electrode is shown. [From Miller & Sherrington (115).]

is a 'pneumotaxic' center located in the pons. These two systems are mutually replaceable and their activity causes periodic inhibition of the inspiratory system and hence rhythmicity in breathing. The location of the pontine pneumotaxic center has recently been explored by Baxter & Olszewski (18) and by Cohen & Wang (42) in 1957, who located it in the dorsolateral portion of the pons. Neurons in this region fire synchronously with respiratory movements in vagotomized animals. Other factors are also involved in the control of respiration, including cortical, hypothalamic and widespread reflex influences of numerous types. There may also be hormonal influences on respiration as shown by Hiestand & Nelson (76, 77).

OTHER REFLEXES. Besides neural organizations in the medulla which are necessary for the control of respiration and cardiovascular activity, this small area contains visceral afferent and efferent mechanisms for various other reflexes. These include the following. *a)* The coughing reflex is mediated by afferent fibers in the vagus nerve and efferent fibers in the nerves to the respiratory and laryngeal muscles. *b)* The sneezing reflex is evoked by afferent fibers which enter the brain stem via the trigeminal nerve. *c)* The swallowing reflex is aroused by stimulation of the trigeminal and glossopharyngeal nerves, the glossopharyngeal and vagus nerves carrying the efferent fibers which arise in the nucleus ambiguus. *d)* The salivary reflex depends on afferent fibers which are borne by the trigeminal and glossopharyngeal nerves and which may be activated by stimulation of oral or olfactory surfaces or by strong psychic factors. Efferent fibers from the salivatory nuclei pass by way of the glossopharyngeal and facial nerves. *e)* The afferents of the sucking reflex are borne by the trigeminal and glossopharyngeal nerves and the efferent fibers by the facial, glossopharyngeal and hypoglossal nerves. *f)* Hyperglycemia may be evoked reflexly. It has been shown by Brooks (34) that the integrity of an area in the lower part of the medulla oblongata is necessary for the occurrence of the elevations in blood sugar which ordinary take place upon the stimulation of afferent nerves. Higher regulatory centers are not necessary for this response. *g)* The vomiting reflex depends on neural mechanisms which have recently been the subject of extensive study; this work has been reviewed by Wang & Borison (170) and Brizzee (32). Vomiting is usually said to be set up through afferent fibers of the vagus, glossopharyngeal, vestibular and possibly splanchnic nerves, by abnormal stimuli in the stomach, pharynx, intestine or inner ear. The efferent fibers are said to originate in the dorsomotor nucleus of the vagus, plus the nuclei for somatic outflow to muscles of the abdominal wall and diaphragm. This reflex concept, however, is evidently too narrow because it is known that vomiting may have other causes. Thus, vomiting occurs in uremia and other disorders which increase the accumulation of metabolites in the body, and also after x-irradiation. Wang, Borison, Brizzee and their colleagues propose that there is a chemoreceptor trigger zone for vomiting in the lower part of the medulla probably in the area postrema. They have found that destruction of this chemoreceptor zone reduces the incidence of vomiting in nephrectomized dogs and cats (30). In studying x-irradiation emesis Brizzee found that severe damage to the dorsal vagal sensory nuclei alone did not eliminate the vomiting. Similar lesions, however, together with involvement of the area postrema did effectively eliminate the response. In vagotomized animals the emesis did not occur, probably because of loss of afferent fibers. Brizzee believes that the area postrema, besides being a chemoreceptor trigger zone, is also a central mediator for incoming sensory fibers. Brizzee & Neal (33) reviewed the cellular morphology of the area postrema, which they found to contain glialoid cells and some small neurons. Some nerve fibers from the area passed toward adjacent nuclei, especially toward the nucleus of the solitary tract. They also observed sinusoids and thick walled arterioles in this region. They postulate that the glialoid cells act as chemoreceptors while the nerve fibers connect with the emetic center in the lateral part of the reticular area in the medulla.

Midbrain

The midbrain appears to contain relatively few autonomic mechanisms although it serves as a route for fibers of passage which are concerned with autonomic activities.

CENTRAL GRAY. The central gray of the aqueduct has been thought to contain centers for circulatory and respiratory regulation, since Sachs (143) in 1911 produced elevation of arterial pressure and increase in respiratory rate from stimulation in this region. More recently Kabat and his collaborators (91, 93, 94) confirmed these findings and also produced pupillary dilatation and contraction of the bladder from stimulation of the central gray and from other points in the tegmentum of the midbrain. Still more recently McQueen *et al.* (114) also obtained pressor

responses from the central gray. This region contains the dorsal longitudinal fasciculus which is considered to be one of the descending pathways for impulses from the hypothalamus. It is well-known that stimulation of the perifornical region of the hypothalamus produces strong autonomic discharges coupled with affective types of behavior. Hunsperger (82, 83) found that lesions of the periaqueductal gray prevented the elicitation of visceral and behavioral responses upon stimulation of the hypothalamus. Skultety (Skultety, F.M., unpublished observations) has recently reviewed the structure and function of the periaqueductal area and has carried out some critical experiments in which he was unable to produce any changes in arterial pressure, gastrointestinal activity or blood sugar by lesions of this area. The principal observed effect seems to be a tendency to diminished affective reactivity and greatly diminished vocal activity. The weight of evidence indicates that this portion of the midbrain is probably in the main a pathway for impulses which subserve autonomic effects.

CONTROL OF URINARY BLADDER. It has been held that the midbrain exerts a control upon the tonus of the urinary bladder. This idea goes back to the experiments of Barrington (16) in 1925, in which bilateral lesions just ventral to the superior cerebellar peduncle were followed by a permanent inability to empty the bladder. Lesions lateral to the posterior end of the aqueduct appeared to yield permanent loss of consciousness of the need to micturate or defecate, although these functions persisted at a spinal level. More extensive lesions sometimes produced increased frequency of involuntary micturition. Tang & Ruch (158, 159) have attempted to determine regions of the brain stem concerned with controlling the micturition reflex in cats. They conclude, "At least four levels of the neural axis . . . influence profoundly the excitability of the sacral micturition reflex, namely, (1) a cerebral inhibitory region, (2) a posterior hypothalamic facilitatory area, (3) a mesencephalic inhibitory area, (4) an anterior pontine facilitatory area (see fig. 18, right, of Chapter XLVIII by Ruch, in this volume). The influence of these areas can be removed successively by the following transections of the neural axis: transhypothalamic decerebration, supercollicular decerebration, intercollicular decerebration and subcollicular decerebration or spinal transection." By using the method of cystometry and experimental lesions after suitable transections, evidence was advanced that a facilitatory area for micturition is located in the mammillary region of the hypothalamus. A bilateral inhibitory area is located in the midbrain tegmentum, just lateral to the central gray, at the level of the superior colliculus; Barrington's pontine facilitatory area is bilaterally located in the dorsal tegmentum at the level of the isthmus just ventral to the lateral angles of the periventricular gray.

We have just seen an example of a system so organized as to exert inhibitory and facilitatory influences on reflexes which can be mediated by a much lower level of the nervous system. It is well-known that the reticular formation contains inhibitory, or suppressor, and excitatory, or facilitatory, mechanisms for somatic reflex action. These are so organized as to make possible the regulation of skeletal muscle tonus and the prevention or occurrence of decerebrate rigidity. We find that the same principle holds for visceral functions of the nervous system. Wang and his coworkers (166–169) have recently carried out a series of experiments on these types of influences as they affect the galvanic skin reflex in cats. They advanced evidence that these facilitatory and inhibitory functions are located at different levels so that the reticular substance of the lower part of the brain stem, which is left after intercollicular decerebration, contains mechanisms for inhibitory influences. These, however, are subject to control from higher levels. Thus, after removal of the telencephalon the galvanic skin reflex is augmented in intensity. This is true also after removal of the forebrain and the thalamus. However, after total removal of the diencephalon there is a slow decline in the reflex with eventual abolition. After intercollicular decerebration there is a sharp fall in intensity and eventual complete loss of the reflex. This is interpreted to mean that the telencephalon normally inhibits the reflex. After thalamic removal, there is an increase in facilitatory influence perhaps from damaged neurons; and, as remarked before, after intercollicular decerebration inhibitory influences are unchecked. In acute decerebrate cats it was found that cooling the medulla or anesthetizing the ventromedial reticular formation restores the galvanic skin reflex which had been abolished by the decerebration; then as the anesthesia wears off, the reflex disappears again as an inhibitory mechanism comes back into activity. It is of interest to note that in a normal animal acute spinal transection at C1 removes excitatory influences and decreases the galvanic skin reflex. In the decerebrate cat, however, this procedure eliminates inhibitory influences and restores the reflex. Turning now to the method of di-

rect stimulation Wang & Brown (167) found that excitation of the ventromedial bulbar reticular formation, the cerebellar anterior lobe, the caudate nucleus and the frontal cerebral cortex inhibits the galvanic skin reflex. The reticular formation has the lowest threshold of stimulation and the greatest inhibitory effect.

Another approach to brain-stem facilitation of autonomic activity has been used by Glasser (63) who found that midpontile decerebration, in cats with sectioned vagi and with carotids tied, produces an increase in arterial pressure and heart rate as well as apneusis and decerebrate rigidity. This increase in cardiovascular activity is attributed to facilitation by the reticular formation.

It also appears likely that some autonomic mechanisms may participate in the bulbar facilitation of somatic reflex activity. Bach (10) finds that stimulation of the bulbar reticular facilitatory mechanism results in liberation of epinephrine and activation of the sympathetic nerve supply to the limb involved. It is not certain that the facilitation so produced is the only mechanism which acts at the site of the reflex arc within the cord.

A converse effect has been described by Dell and his co-workers (44) who have found activation of the upper midbrain reticular formation by epinephrine which in turn leads to a generalized activation of the upper portion of the brain. This humoral mechanism may be important for arousal from sleep. There is also evidence that the sympathetic nervous system acts on facilitatory and inhibitory functions of the reticular formation in motor activity, and that afferent impulses from the pressor receptors of the carotid sinus may have inhibitory effects here. It has been shown that the midbrain and hypothalamus contain significant amounts of sympathin (162). Indeed, these regions contain the richest supply of sympathin in the entire brain of the dog, and Dell presents arguments for an adrenergic type of transmission in this part of the brain.

Dell points to the regulation of blood sugar as an example of autonomic neurohormonal interaction which is based on the existence of reserves of glycogen in the liver and muscles. When these reserves are diminished, there is an augmentation of the secretion of epinephrine and increase in its level in the blood. As a result the following events occur: wakening, augmentation of muscular activity even to the point of hyperactivity, intensification of sensory attention so that the animal develops a drive to satisfy its need for food. Fundamental mechanisms for the transformation of organic needs into behavior thus appear to be represented in this portion of the brain. Another chemical feed-back mechanism may be constituted by the fact that any sensory mechanism which is concerned with the arousal of the emotional response may feed into the reticular formation, including of course the hypothalamus, and provoke discharges which bring about the release of epinephrine and norepinephrine. This in turn, acting on the reticular formation, can augment and prolong the activity of the elements of this system up to the time when the circulating hormone has been destroyed. As Dell points out, this may offer some explanation as to why it is usually very difficult to arrest or confine an emotional state.

Although the midbrain is not usually held to be of particular importance in the autonomic scheme, aside from elements in the oculomotor and perhaps the trigeminal complexes, and aside from the somewhat indefinite centers controlling tonus in the rectum and bladder, we have seen that this area besides its importance as a transmitter of autonomic impulses may play a role in autonomic integration. Part of this role is dependent upon hormonal influences.

AUTONOMIC FUNCTIONS OF OCULOMOTOR NERVE. It is usually held that the preganglionic fibers for the innervation of the constrictor muscle of the pupil and of the ciliary muscle originate in the nucleus of Edinger and Westphal which overlies the main oculomotor nucleus, and that these fibers enter the oculomotor nerve and terminate in the appropriate eye muscles. According to Olszewsky & Baxter (128), however, the evidence that these fibers originate in the Edinger-Westphal nucleus is relatively scant.

Beside the visual afferent influences which bring about the pupillary light and convergence reflexes, afferent impulses of extraocular origin play an important role in control of the pupil. Thus pupillary dilatation occurs in response to noxious stimulation and emotional excitement. This is in part due to activation of dilator pupillae muscles through the cervical sympathetic. However, there is evidence, originally advanced by Ury & Gellhorn (60), that there is some central inhibition of the pupilloconstrictor mechanism.

DIENCEPHALIC AUTONOMIC MECHANISMS

The modern student of neurophysiology is all too aware that there is a region called the hypothalamus which, he has been led to believe, plays a key role in

the regulation of autonomic activities. To a large extent this is true, but he sometimes forgets that this region is a part of a much more extensive system of neurological circuits. It is true that here we have a condensation of fibers of passage conveying impulses from higher and lower regions and that here are 'integrated' many converging influences, so that the product conforms to a pattern suitable for the needs of the organism. These neural patterns may be reintegrated at a lower level of the brain stem and their effects are eventually consummated by the spinal cord complexes.

Anatomy of Hypothalamus

It is perhaps suitable to summarize briefly the structure, relationships and connections of this region as they are understood today (84, 85). Some of these structures are shown in figure 2 of Chapter LXIII of this work devoted to neurological mechanisms in emotion. Mitchell (121) remarks, ". . . anyone who suffers from the delusion that anatomy is an effete subject with no problems left to solve is advised to read even a tithe of the bewildering conglomeration of literature on the hypothalamus and its connections. If he does delusion will be replaced by disillusion." As this region has become more accessible through the use of modern technicological developments, it is possible increasingly to fit in its activities with those of other parts of the central nervous system. We can also take a more disinterested view of its nuclear configuration because, while this region contains a number of well-defined morphologically distinguishable groups of neurons, embedded in a background of nerve fibers and diffusely scattered neurons, only two or three of these cell groups may be related to any specific function. As a matter of fact, areas of the hypothalamus seem to be more important than nuclei. However, since some nuclei do have definite functional relationships and since their designation is important from the standpoint of orientation, providing a means of communication between the experimentalists, and because in the future this nuclear classification may become of unforeseen importance, a brief description of the hypothalamus is herewith included.

SUBDIVISIONS OF HYPOTHALAMUS AND THEIR NUCLEI. The hypothalamus is bounded anteriorly by the lamina terminalis which of course includes the anterior commissure. Here is located the preoptic region, providing a zone of transition between the subcallosal septal region and the hypothalamus. The posterior boundary coincides with the interpeduncular fossa. Dorsally we have the hypothalamic sulcus marking the boundary between hypothalamus and thalamus. Inferiorly we have the optic chiasma and behind it, the floor of the third ventricle which includes the infundibular stem. The two halves of the area are of course separated by the ventral extension of the third ventricle. The hypothalamus caudal to the preoptic area seems logically divided into supraoptic, tuberal and mammillary regions, each of which contains several nuclei.

a) In the supraoptic area, the anterior hypothalamic nucleus is well-defined in some forms but more vague in man in whom it is simply an area dorsal to the optic chiasma. Embedded in it just above the chiasma at the edges of the supraoptic recess is the suprachiasmatic nucleus. The paraventricular nucleus is a triangular group of darkly staining cells gathered along the sides of the ventricle and extending somewhat laterally at its dorsal extremity. The other conspicuous group in this region is the supraoptic nucleus which overlies the beginning of the optic tract and extends a short distance posteriorly from it in the direction of the infundibular stem. This also contains large dark-staining neurons, and these as well as those of the paraventricular nucleus have certain cytological characteristics which indicate that they may be capable of secretory activity.

b) The second region is the tuberal portion of the hypothalamus. This may be divided into a medial and a lateral region. The lateral area is marked by its heavy content of nerve fibers, both myelinated and unmyelinated, many of which pass through the hypothalamus in a rostrocaudal direction. These fibers constitute the medial forebrain bundle, much of which arises in the olfactory regions farther forward and which runs back into the tegmentum of the midbrain. It also contains fibers from the hypothalamus which descend and contributes, in its turn, connections to the hypothalamic neurons. Through much of the extent of this nucleus there are small undifferentiated neurons; but, especially in the more caudal reaches, a large number of large dark-staining cells are found, rather irregularly grouped. These are especially conspicuous in man and may be important as contributing fibers to the descending connections of the region. Other groups of small neurons, known as the lateral nuclei of the tuber, occur in man but are found only with difficulty in lower forms. The separation between the lateral and the medial areas of the tuberal region is marked by the descending column of the fornix, around which the neurons compressed by its passage have sometimes been called the perifornical nucleus. Actually, perifornical area would be

a better term. The medial part of the tuber contains two rather large groups, the dorsomedial and the ventromedial nuclei. The dorsomedial is rather vague and contains a mixture of neurons most of which are rather small. The ventromedial nucleus is quite conspicuous in carnivores and the lower primates. It is an oval mass of small cells which are compactly grouped in lower forms but which in man have a much more diffuse arrangement. Ventrally, the so-called arcuate nucleus lies at the lateral edges of the ventral extremity of the third ventricle, near the median eminence. Extending dorsally along the walls of the ventricle in this region are thin layers of small neurons, many of them poorly differentiated, which are grouped as a periventricular nuclear system. In the posterior part of the tuberal region and extending to the most posterior portion of the hypothalamus is the posterior hypothalamic nucleus or area. This lies between the two converging mammillothalamic tracts. It is very similar in structure to the lateral hypothalamic region, being a melange of large and small cells. This region is important because of its contribution to descending hypothalamic connections and because in experimental work lesions in this region epitomize some of the effects of more extensive lesions in the anterior areas.

c) The third portion of the hypothalamus is the mammillary area. This is marked principally by the presence of the bulging mammillary bodies which contain a complex of nuclei. A large oval medial nucleus is separated from a lateral nucleus, of larger and darkly-staining cells, by an intercalated nucleus. Anterior to the mammillary nuclei is the premamillary region which, in lower forms at least, is marked by another complex of small nuclear groups, not very conspicuous in man. They appear to receive fibers ascending from the tegmentum in the mamillary peduncle.

AFFERENT CONNECTIONS. A great deal has been written concerning the fiber connections of the hypothalamus, and there is reasonably good evidence for the following afferent connections of the primate hypothalamus. *a)* The medial forebrain bundle, which contains olfactory, parolfactory, septal and striohypothalamic fibers, may be mentioned first. The septohypothalamic fibers probably relay impulses from the frontal lobe of the cerebral cortex and perhaps also impulses originating in the rhinencephalic regions. *b)* The thalamohypothalamic fibers, which arise chiefly from the medial and mid-line thalamic nuclei and run principally by way of the periventricular system, may be important for relaying somatic and visceral sensory impulses to the hypothalamus. These connections probably also set up the major afferent connections between the neopallial cortex and the hypothalamus, for the dorsomedial thalamic nucleus shows degeneration after prefrontal lobotomy and also after hypothalamic lesions (164). Although direct connections from the orbitofrontal regions of the hemisphere to the ventromedial nucleus of the hypothalamus have been described, more recent work with modern degeneration techniques has not supported this finding (9). *c)* The fornix is a prominent bundle which arises in the hippocampus, terminates in the mammillary nuclei and probably also sends some fibers into other hypothalamic nuclei (126). *d)* The stria terminalis, which arises from the amygdala, appears to have connections with the preoptic regions, perhaps with the septal area, and has a rather diffuse distribution in the hypothalamus. The chief evidence for these connections is based on comparative studies of lower animal forms. *e)* Pallidohypothalamic fibers constitute a well defined bundle which arises in the lentiform nucleus and appears to terminate in the ventromedial hypothalamic nucleus. Other connections with the globus pallidus by way of the ansa lenticularis are also possible. *f)* Subthalamohypothalamic connections are probably mediated by fibers from the nucleus subthalamicus, chiefly crossed. *g)* The mammillary peduncle rises in the mesencephalon and ends in the lateral mammillary nucleus. Its existence in man is questionable. *h)* Vagosupraoptic connections, which have been demonstrated physiologically (39, 145), presumably arise in the nucleus of the solitary tract, but whether they set up direct or indirect connections with the hypothalamus is not known.

EFFERENT CONNECTIONS. Efferent connections of the hypothalamus may be summarized as follows. *a)* Hypothalamothalamic fibers include the mammillothalamic tract which extends from the mammillary nuclei to the anterior thalamic nuclei which in turn are connected with the anterior part of the limbic cortex (gyrus cinguli), and periventricular fibers, presumably connecting with the dorsomedial thalamic nucleus which in turn connects with the frontal cortex. *b)* The mammillotegmental tract descends to the deep tegmental nucleus of the lower brain stem. *c)* The periventricular system and the dorsal longitudinal fasciculus are important for conduction of descending impulses. These fibers may arise throughout the hypothalamus, but the posterior

hypothalamic area contributes especially to this system. Some of these fibers descend through the central gray of the aqueduct; others fan out into the tegmentum. *d)* Diffuse descending connections, which extend caudalward in large part as continuations of the medial forebrain bundle, probably arise throughout the hypothalamus, although the posterior and lateral areas probably are the chief contributors. This system of fibers is scattered in the lateral portions of the tegmentum (104, 107), and physiological experiments indicate that it is of prime importance in the conduction of hypothalamic impulses toward the lower autonomic centers. *e)* Hypothalamohypophysial connections are made through supraopticohypophysial fibers which arise from the main and accessory groups of the supraoptic nucleus and terminate in a rich branching plexus in the neurohypophysis, paraventriculohypophysial fibers which arise in the paraventriculus nucleus and end in the neurohypophysis, and tuberohypophysial fibers which arise from scattered neurons in the tuberal region. It is likely that some of these fibers terminate in the median eminence and in the infundibular stem. It may be noted here that many of these neurons give evidence of neurosecretory activity. *f)* A diffuse projection system to the cortex originates in the posterior portion of the hypothalamus and in the nearby reticular formation of the mesencephalon. This system, which probably involves thalamic relays, is important in the maintenance of the waking state (105). It will be noted that included in the above efferent systems are rich connections with the neopallium, with the orbitofrontal cortex and with rhinencephalic structures. These provide an ample basis for elaborate feed-back mechanisms and reverberating circuits (64).

It is readily apparent that this small area is distinguished by the richness of its fiber connections. It is quite likely that the influence of the cerebellum is also brought to bear on the hypothalamus, although the pathways are not well known. The afferent and efferent systems involved in the total hypothalamic-reticular formation picture are probably still more complex than is indicated by the above summary, and the intermingling of these cells and fibers has placed great obstacles in the way of experimental exploration.

Functional Considerations of Hypothalamus

Although the hypothalamic region was a relatively large part of the brain in primitive vertebrates, evolutionary development of the higher mammals has almost completely enveloped it with folds of forebrain. It is not surprising then that the physiological significance of this remote area escaped analysis until recently. Interest in endocrine physiology directed attention to the hypophysis, and the spectacular experiments of Cushing and others first obscured and later overemphasized the nearby hypothalamus, for there was at one time considerable confusion in regard to the respective functional relationships of these structures. We now know that nervous control of the pituitary, so far as it exists, is mediated through the hypothalamus and that the latter participates in certain functions which were once thought to be exclusively hypophysial.

There is danger in thinking of the hypothalamus as a distinct and isolated structural entity. We have seen that it has direct and indirect nervous connections with many other parts of the brain, including the cerebral cortex, and from the functional viewpoint it probably should not be considered as separate from other diencephalic and lower brain-stem mechanisms. We have already seen how the hierarchy of autonomic mechanisms is functionally interrelated in the spinal cord and lower brain stem. The so-called autonomic phenomena with which the hypothalamus seems especially concerned are also related to other parts of the forebrain, as well as the mid- and hindbrain, and hypothalamic functions are probably largely integrative. The hypothalamus, then, fits into large schemes, some of which are not exclusively autonomic and which involve certain patterns of behavior, including sleep-waking phenomena and some aspects of emotional activity.

Analysis of the participation of the hypothalamus in autonomic activities began with the work of Karplus and Kreidl who, as early as 1909, studied the effect of stimulating the wall of the third ventricle in animals. In recent years various modifications of this approach, as well as the use of experimental lesions, have been reapplied many times in carnivores and primates, including man, by such investigators as Hess, Ranson and many others. To summarize briefly, readily elicitable and observable responses to electrical stimulation include: elevations of arterial pressure, cardiac acceleration, dilatation of the pupils, sweating, piloerection, hyperglycemia and cessation of gastrointestinal movement. The responses obtained are not exclusively sympathetic, however, for with different forms of electrical stimuli (68, 69), and especially from the more anterior regions, parasympathetic phenomena may be produced. These include bladder contraction, increased gastrointestinal

motility, cardiac depression and vasodilatation. While attempts have been made to delineate separate parasympathetic and sympathetic areas in the hypothalamus (20, 21), there appears to be considerable mingling of the elements responsible for these responses throughout the hypothalamus. Responses are in general most easily obtained from the lateral hypothalamic area, which is relatively rich in fibers and poor in neurons.

Granted that these striking results may be obtained by stimulation of the hypothalamus we would not be justified in assigning to this region the predominant role in producing such effects in normal life. Similar results can be obtained from stimulating many other regions, including the limbic and orbitofrontal regions of the cerebral cortex, as well as the motor areas of the frontal lobe. Nevertheless, these responses are most easily provoked from the hypothalamus. When they are obtained by stimulation of this region in unanesthetized animals, the sympathetic components are usually associated with patterns of behavior which have all the appearance of rage and fear (73, 75, 92). This type of observation in man has been rare and restricted, but cardiac acceleration has been observed upon electrical stimulation of the anterior part of the human tuber cinereum (173). While cardiac depression followed stimulation of the preoptic area, there were no signs of emotional stress but rather a tendency to drowsiness and unconsciousness. In other cases, however, in which the walls of the third ventricle were manipulated at operation or were irritated by small tumors, violent autonomic discharges have been seen, sometimes accompanying manic behavior (40, 130). Recently Segundo and his co-workers have stimulated the fornix and the wall of the third ventricle in human patients and observed expiratory apnea and occasional clouding of consciousness from the fornix while stimulation of the wall of the third ventricle produced polypnea.

Assuming that the hypothalamus participates in the initiation of such specific autonomic effects, it is easy to see how certain of these alone or in combination may take part in more general functions. These include regulation of body temperature, regulation of some activities of the posterior and anterior lobes of the pituitary, regulation of appetite and perhaps thirst, reinforcement of the waking state, facilitation of somatic motor activity, and integration of the behavior patterns of certain emotional states. Brief discussions of these follow.

BODY TEMPERATURE CONTROL. Complete destruction of the hypothalamus in lower mammals and in man practically abolishes all temperature control and allows the body temperature to fluctuate with environmental variations. Destruction of the anterior part of the hypothalamus (the preoptic and supraoptic regions) abolishes the heat loss mechanisms which include peripheral vasodilatation, sweating and panting (139). Subjects are unable to defend themselves against high environmental temperature; the posttraumatic and postoperative hyperthermias which follow injury to the base of the brain are in this class. It has been shown experimentally that heating the blood which bathes this area elicits the usual heat disposal responses, and the descending nervous pathways involved have been described (106). Heat production and conservation are controlled by more caudal regions of the hypothalamus, but precise location of the structures involved is not yet possible. Since bilateral lesions in the posterior regions of the hypothalamus also involve the descending paths for heat disposal, such lesions are as effective in producing poikilothermia as is complete hypothalamic destruction. A careful attempt to segregate the various mechanisms for temperature regulation was made by McCrum (113). While it was confirmed that the heat disposal mechanisms are largely concentrated in the anterior part of the hypothalamus, it was also found that there is considerable intermingling of the 'thermostatic' neurons and it is impossible to draw a sharp line of distinction between separate areas. Birzis & Hemingway (28) have found that the lateral hypothalamic area participates in the evokation of shivering. The descending pathway mediating shivering descends through the midbrain just lateral to the red nucleus, into the lateral part of the reticular formation of the midbrain, pons and medulla oblongata, and into the lateral funiculus of the spinal cord. Inhibition or suppression of shivering may be produced by stimulation in the hypothalamus and midbrain, the most sensitive area being the preoptic region. Hemingway and his co-workers (72) propose that this effect is a means for suppression of shivering when the musculature is needed for skeletal movement. Perhaps this mechanism participates in the inhibition of shivering which occurs upon stimulation of peripheral nerves as shown by Boyarsky & Stewart (31). Further discussion of the nervous mechanism of temperature regulation may be found in Chapter XLVI of this work by Ström.

Since the basal metabolic rate is involved in heat production, it may be mentioned that basal metabolism falls after destruction of the hypothalamus. It has also been shown that activation of the thyroid during exposure to cold is a function of the hypo-

thalamus (160). These functions are undoubtedly conjoint with the anterior pituitary, and Bogdanove & Halmi (29) have shown that bilateral lesions in the anterior part of the hypothalamus suppress the formation of thyrotrophic hormone by the former and block the goitrogenic effect of thiouracil.

HYPOTHALAMICOHYPOPHYSIAL RELATIONSHIPS. It is certain that not all functions of the hypophysis are under nervous control, especially those of the anterior lobe which is able to respond to chemical feed-back mechanisms such as changes in blood concentration of various hormones from other endocrine glands. It is also likely that such nervous control as exists may vary in different animal forms. There is, however, evidence of nervous participation in the regulation of the functions of both of the chief lobes. Chapter XXXIX of this work is devoted to this subject.

a) The Posterior Lobe. The posterior lobe is chiefly concerned with water metabolism, although a substance which promotes contraction of smooth muscle is also formed within it. An antidiuretic hormone which promotes reabsorption of water in the distal convoluted portion of the renal tubule against the osmotic influences of the blood is formed and released in the posterior lobe and its stalk. Production of this powerful substance depends upon the integrity of nerve fibers which originate from the supraoptic nucleus. There have been two theories concerning the production of this hormone. The first proposes that nerve impulses conveyed by fibers of the supraopticohypophysial tract bring about the production and release of the antidiuretic hormone by the pituicytes which are glia-like cells peculiar to the posterior lobe. Against this theory is the fact that after degeneration of the supraopticohypophysial tract there is no change in the characteristics of these cells.

Another theory, supported by Scharrer (147) and others, proposes that the neurons and fibers of the supraopticohypophysial tract actually form and secrete the hormone. This theory is based in the first place upon the occurrence of a stainable substance within the cell bodies and axons of these neurons. This neurosecretory substance may be a forerunner of the antidiuretic hormone, it may be a carrier for the antidiuretic hormone or it may interact with the pituicytes in the production of the antidiuretic hormone. This hormone has been extracted from the supraoptic region of the hypothalamus, and sectioning or occlusion of the pituitary stalk produces a damming back of the secretory material which ordinarily is presumed to work its way out along the axons to the fiber endings. While the neurosecretory material has not been positively identified with the antidiuretic hormone, some histochemical attempts have been made to check this possibility. Barrnett (17) found disulfide groups in the hypothalamicohypophysial fibers in the stalk and in the infundibular process in dogs and rats. In extracts of the neurohypophysis, insoluble pituitrin also stained for disulfides. Sloper (155) and Adams & Sloper (1) have recently advanced histochemical evidence that the neurosecretory material has a close similarity to the cyclic octapeptides of du Vigneaud. While not completely proved, the neurosecretory theory is extremely attractive and fits very well with modern ideas concerning the regulation of urine output, including the phenomena of diabetes insipidus. The subject is further considered in Chapter XL of this work by Ortmann.

There is now ample evidence that diabetes insipidus, which is characterized by excretion of large quantities of dilute urine, is due to degeneration of the supraopticohypophysial system, to interruption of these nerve fibers high in the pituitary stalk, or to the destruction of the posterior lobe together with the stalk (51). Experimental findings in animals have been amply confirmed by observations on human patients (67). If all sources of antidiuretic hormone are completely eliminated, diabetes insipidus will occur even if the anterior lobe of the pituitary is absent; but polyuria is never maximal under these circumstances. A maximal polyuria depends upon normal levels of metabolic activity throughout the body, and these depend upon normal anterior lobe function. Diabetes insipidus in itself is probably not associated with abnormalities of salt metabolism. The latter may occur, however, with other types of lesions of the hypothalamus which depress the appetite for fluids. Application of the neurosecretory theory to this condition accounts for the survival of the pituicytes in otherwise degenerated infundibulohypophysial structure.

There is excellent evidence that the rate of production of antidiuretic hormone varies in accord with changes in osmotic pressure of the blood (161). Increase in the osmotic pressure of the blood which supplies the supraoptic nuclei increases the activity of these neurons and increased amounts of antidiuretic hormone are released to meet the need for water conservation. It is interesting to note in this connection that the paraventricular and supraoptic nuclei have an exceedingly rich blood supply. Verney has hypothecated the existence of osmoreceptors in

this part of the hypothalamus and Jewel (89) has described neurons in the supraoptic nuclei which contain large vesicles, the contents of which are not known. However, one questions whether the existence of such osmoreceptors is necessary if these neurons resemble functionally those of the respiratory mechanism in the medulla in being sensitive to changes in the ambient fluids. There is also evidence that the activities of the supraopticohypophysial system may be modified by nervous means. In the stress produced by noxious stimulation there is an increased production of antidiuretic hormone (120), and it is very likely that its production and release may be modified by psychic influences.

The paraventricular nucleus has recently been associated with the production of oxytocin by Olivecrona (127). After bilateral destruction of the paraventricular nuclei in rats by small lesions no oxytocin was produced. These lesions had no effect on the production of vasopressin nor on the thyrotrophic and adrenotrophic activities of the anterior lobe. That the oxytocin also proceeds along the nerve fibers into the posterior lobe is indicated by the findings of Moreno *et al.* (123) who found that extracts of the tuber cinereum made soon after hypophysectomy in rats showed oxytocic potency twice as high as that observed in tuber extracts of animals hypophysectomized after being killed.

b) Anterior Lobe. The neural control of the anterior lobe of the pituitary has provided the subject matter for a fascinating current chapter in neuroendocrine physiology. This subject has been reviewed recently by Harris (70), Fields *et al.* (50), Benoit & Assenmacher (22), Hume & Wittenstein (81) and is discussed in Chapter XXXIX of this work by Harris. However, for the sake of completeness a brief comment on this relationship will be included here. It is well known that massive lesions of the hypothalamus tend to depress general anterior lobe functions. More discrete lesions in lower animals produce changes in the sex cycle. Thus lesions in the anterior region may be followed by prolonged cycles or even constant estrus, while posterior lesions abolish the cycles. In animals which ovulate only after copulation, lesions of the pituitary stalk or of the tuber cinereum prevent ovulation. Apparently the neuromechanisms producing ovulation in these forms work through the hypothalamus. The route by which the anterior lobe could be affected by these procedures poses a troublesome question because practically no nerve fibers pass from the hypothalamus to the anterior lobe. There is, however, good evidence for the existence of a venous portal system through which hormone-like chemicals released into the blood by hypothalamic secretory neurons may be brought into contact with anterior lobe cells (66, 175). While the primary blood supply of the hypothalamus and that of the hypophysis are anatomically distinct, the hypophysial arteries supply a capillary network of the median eminence of the stalk of the pituitary from which a system of veins is in turn formed. These veins communicate eventually with the sinusoids of the anterior lobe. In the neurosecretion theory it is held that neurohumoral substances, produced by hypothalamic neurons and released from the processes of these neurons, enter the blood of the capillaries of the stalk and median eminence. After passing through the portal channels, they exert direct chemical effects upon the gland cells of the anterior lobe. These humoral substances, which apparently are adrenergic, when released in sufficient quantities into the portal blood stream are thus proposed to induce the formation or release of appropriate anterior lobe hormones.

While much evidence exists for the neural regulation of both gonadal and adrenocortical functions of the pituitary, it remains to be seen whether other hypophysial activities may also be influenced by the hypothalamus. Thus we may ask if excessive anterior lobe secretion may be so produced by neurohumoral stimuli that diabetes mellitus, acromegaly, gigantism, hyperthyroidism and exophthalamos can result. In this connection, it should be recalled that thyroid activation by cold is brought about through hypothalamicohypophysial activity. Thus lesions in the anterior part of the hypothalamus in rats depress the thyrotrophic function of the anterior lobe, and it has already been mentioned that such lesions block the thiouracil effect upon the thyroid (29). A curious aside here is the fact that after such lesions there is a remarkable increase in mitotic activity in the completely mysterious pars tuberalis of the pituitary.

While considering hypothalamic-pituitary relations carbohydrate metabolism should be mentioned. The important role of the anterior lobe as a regulator of sugar metabolism needs no elaboration here. While the participation of the hypothalamus in such affairs has been somewhat uncertain, changes in carbohydrate utilization have been noted clinically in many cases of hypothalamic disease; and there is good evidence that in animals certain hypothalamic lesions may alter the course of experimental diabetes mellitus so that insulin requirement is reduced (43, 84). Lesions in the posterior part of the

hypothalamus and perhaps in the upper part of the midbrain may lead to an increased sensitivity to insulin (157). Since profound disturbances in growth occur in rats with such lesions, some evidence is added that the anterior hormone concerned with carbohydrate metabolism is related to the growth hormone; and the administration of the growth hormone appears to reduce the insulin sensitivity of experimental animals with hypothalamic lesions. The lesions which ameliorate experimental diabetes mellitus or increase sensitivity to insulin may be widely varied and scattered, and careful examination of these lesions in the hypothalamus in a large number of animals by the author and his colleagues has not presented any evidence of specific localization. The results suggest, however, that hypothalamic injury may disturb the production or release of such pituitary principles as are concerned in carbohydrate metabolism.

Hypothalamus and Behavior

We are here concerned with such types of behavior patterns as are involved in sexual activity, the securing of food, generalized emotional responses and states of wakefulness and sleep.

SEXUAL BEHAVIOR. There are cases, both clinical and experimental, in which sexual behavior is abnormal or deficient even in the presence of an intact pituitary and gonads. Experimental work indicates that the estrual behavior pattern does not appear in animals in which the caudal portion of the hypothalamus, plus the upper part of the midbrain, have been destroyed despite administration of pituitary or gonadal hormones in quantities sufficient to arouse sexual behavior in normal animals (13). Normal patterns of sexual activity may appear upon hormonal treatment after removal of the neocortex and much of the olfactory areas, however. In human individuals, cases of idiopathic amenorrhoea and frigidity have frequently been ascribed to emotional disturbances which may possibly interfere with hypothalamic activation of the pituitary (6). It has been noted above that sufficiently extensive lesions of the posterior part of the tuber may produce gonadal atrophy. It must not be forgotten that normal sexual behavior depends upon neural patterns activated or otherwise influenced by appropriate hormones. This subject is considered further in Chapter XLIX of this volume by Sawyer.

APPETITE AND OBESITY. The classical description of adiposogenital dystrophy as a hypothalamic phenomenon is very familiar and the term 'hypothalamic obesity' has received much use. It is true that obesity may be associated with hypothalamic disease, often caused by encroachment by hypophysial tumors, and so may genital dystrophy; but the two are not necessarily inseparable. It is likely that both lower food requirements and overconsumption of food contribute to hypothalamic obesity. There is excellent evidence that experimental lesions in the ventromedial portions of the tuber in animals are associated with excessive, even ravenous appetite and with hyperphagia which result in extreme obesity if unrestricted access to food is permitted (86). It is not clear whether this gluttonous disposition is due to changes in visceral activity or whether satiety may be prevented, or appetite released or facilitated by these lesions. The lesions may be quite restricted and have been found invariably to be within the boundaries of the ventromedial nuclei. Striking evidence that this nucleus may be concerned in appetite or satiety is presented by Marshall *et al.* (110) who injected gold thioglucose in a certain strain of mice. This substance caused extensive damage to the ventromedial nuclei with resulting obesity.

If a balance exists between an inhibitory zone in the ventromedial nucleus and a separate activating mechanism for appetite, the question arises as to where the latter may be located. Anand & Brobeck (5) have presented evidence that bilateral destruction of rather small areas in the lateral hypothalamic region does away with appetite, and it has been known for some time that extensive lateral and posterior hypothalamic lesions are not consistent with voluntary taking of food. Larsson (101) stimulated the lateral hypothalamic regions in goats and produced hyperphagia; during the actual stimulation, oral feeding pattern movements were elicited. Forssberg & Larsson (54) studied the distribution of certain injected isotopes in the hypothalamus in hungry and fed rats and found evidence for increased absorption of such isotopes in this area in hungry animals. They suggest that changes in the concentration of adenosinetriphosphate and creatine phosphate in the region may be a driving force for appetite.

A somewhat similar mechanism for drinking behavior has been postulated. Andersson & McCann (7, 8) found that stimulation in the dorsal hypothalamic region in goats caused increased drinking as well as evidence of milk ejection and antidiuresis. They also found that certain lesions in dogs would produce hypodipsia. Greer (66) also found that

periodic stimulation of the hypothalamus in rats was associated with increased drinking.

There is usually some decline in metabolism and in general bodily activity in animals with lesions of the ventromedial nuclei but not enough to account for more than a limited portion of the positive food balance because the obesity can be controlled to a great degree by restricted diet. If the lesions are sufficiently extensive, there may also be gonadal atrophy. On the other hand, with restricted lesions the gonads may remain quite normal. It is of considerable interest that very frequently these obese and hyperphagic animals develop a state of 'savageness.' Appetite and thirst are considered in Chapter XLVII of this volume by Brobeck.

PATTERNS OF EMOTIONAL BEHAVIOR. It has long been known that patients with lesions encroaching upon the diencephalon occasionally have spells of senseless crying or laughing unassociated with appropriate subjective feelings. Neurosurgeons manipulating the hypothalamic region in patients without general anesthesia have noted manic outbursts. Stimulation of suitable areas of the hypothalamus in unanesthetized animals evokes an expression of rage accompanied by all the usual autonomic phenomena (74, 92) which quickly subside when stimulation ceases. Such responses are most easily produced by stimulation of the lateral hypothalamic area near the fornix. Autonomic signs include pupil dilatation, horripilation, and sometimes urination and defecation. It is said that response patterns of this type do not become conditioned, but there is recent evidence that animals will attempt to avoid receiving stimuli of this type (41). The response may be greatly reinforced if the animal sees persons or objects at which it can be directed and an actual attack may result.

Somewhat similar, but almost paroxysmal, rage reactions may be observed in animals after removal of large areas of the forebrain. Such behavior develops in response to innocuous external stimuli, is ill-directed, subsides quickly and has been called 'sham rage.' Again all the usual autonomic components accompany the somatic response (12). The complete picture of sham rage does not appear unless the posterior part of the hypothalamus is intact. Incomplete rage may, however, appear after massive hypothalamic destruction in animals with intact forebrains.

After relatively restricted bilateral lesions in the region of the ventromedial nuclei, animals may become extremely, chronically and incurably savage, developing a malevolent attitude towards men and other animals which is not unmixed with fear reactions (86, 172). During times of violent affective response, all usual overt signs of autonomic discharge are seen. When undisturbed, the activity level is subnormal. Animals with such behavior frequently show gluttonous appetites as mentioned previously and become very obese, but this is not an invariable correlate of the changed behavior pattern.

We have here a situation in which loss of the forebrain and the presence of the hypothalamus predisposes to senseless rage responses to mild stimuli while, on the other hand, appropriate lesions of the hypothalamus in otherwise intact brains effect a complete change in attitude and personality, typified by well-directed defensive and offensive attitudes, and crowned by the appearance of extreme anger with all of its autonomic correlates. This pattern of disturbed personality and behavior following restricted basal lesions may be considered as a true organic psychosis.

The locations of the mechanisms released by these lesions have not been determined and the areas involved may be extensive. Hunsperger (83) has found that lesions of the periaqueductal gray matter prevent the occurrence of the rage pattern in response to hypothalamic stimulation. Whether this involves simply a descending pathway for the total pattern response is not clear. The rage and savageness associated with ventromedial lesions has not as yet been found to be prevented by lesions of the piriform areas which ordinarily produce very bland and tame animals (149). Nor does administration of ataractic drugs eliminate the savageness. It is interesting that brain injuries in this region in man are often associated with personality changes and swings of mood between euphoria and depression, aggressiveness, Korsakoff-like responses (140) and paranoid delusions. The operation of prefrontal lobotomy for depressed and withdrawn psychotic patients has been in part predicated on release of hypothalamic influences from suppression exerted by the prefrontal cortex. On this basis efforts have been made to obtain similar results by producing bilateral lesions in the dorsomedial thalamic nuclei in such patients (156, 176). It will be recalled that the latter nuclei participate in communication between the frontal lobe and hypothalamus.

If alterations in emotional behavior patterns can result from disturbed hypothalamic-forebrain circuits or from restricted lesions within the hypothalamus, what happens to the emotional patterns if the hypothalamus is destroyed or its descending efferent elements are destroyed or interrupted? In higher mammals destruction of the hypothalamus produces a somnolent, semicomatose animal with profound lack

of motor initiative, loss of appetite and serious defects of visceral function and body temperature control (85, 87). The animals can be aroused from the somnolent state for brief intervals and rough handling may evoke defensive behavior at times. Survival time is relatively short, in terms of days or weeks, even with careful nursing. Lesions restricted to the posterior part of the hypothalamus which interrupt the descending and ascending fiber connections yield a similar picture, with the somnolence and loss of affective response being especially marked. If there is also involvement of the upper end of the adjacent midbrain in cats, motor activity may be greatly depressed and spastic states ensue. These animals may retain their somnolence for some weeks but may finally have periods of wakefulness, especially when unfed, or when bowel and bladder are full.

Experimental lesions involving the rhinencephalic (limbic) systems have also produced marked disturbances in behavior (14, 98, 149). Thus lesions of the piriform areas in a wide variety of species have been found to produce bland, tame, often hypersexual animals (149). Other regions nearby have been destroyed by Bard & Mountcastle (14) and the subsequent development of savage behavior described. It will be recalled that important functional connections exist between the limbic system and the hypothalamus. Many of these connections are multisynaptic, although some direct connections from the amygdala have been described, chiefly by way of the stria terminalis. A very well-known and conspicuous connection is provided by the fornix which arises from the hippocampus, ends in various places in the hypothalamus, but especially in the mammillary body, which is then connected with the anterior thalamic nuclei by the mammillothalamic tract. This thalamic region is connected with the anterior part of the gyrus cinguli. In our experience, bilateral lesions of the fornix and of the mammillary bodies in cats have not led to any very striking behavior change except perhaps an increased euphoric response to petting. However, in man, lesions of the mammillothalamic system have been described in cases of Korsakoff's syndrome (140). The physiology and autonomic relationships of the limbic and associated systems are discussed in Chapters LVI, LVII and LVIII of this work and, therefore, need no further consideration here.

SLEEP-WAKING MECHANISMS. As has been noted, experimental lesions of the posterior part of the hypothalamus produce somnolence and deep sleep. This sleep has many characteristics of normal sleep in that it is to a certain extent reversible if sufficiently strong stimuli are used. It is well-known that the pathological sleep of encephalitis lethargica may be associated with lesions of the walls of the third ventricle and upper end of the central gray of the aqueduct. The subject of sleep has an extensive literature and the present consideration must be very brief. Philosophically speaking, it seems that attention should be directed at the state of wakefulness, for sleep is, in part at least, just a condition which occurs in the absence of wakefulness. The factors which contribute to maintenance of wakefulness are extrinsic and intrinsic. Extrinsic factors involve streams of afferent impulses derived from exteroceptive and interoceptive stimuli. When the number or intensity of such impulses is sufficient, activation of the cerebral cortex necessary for the waking state is produced. This change in cortical activity is well shown by the arousal or activation type of change seen in the electrocorticogram. These streams of direct afferent impulses may be maintained by a variety of types of stimuli: light, sound, pressure, heat and cold, distention and the like. It is obvious that the intensity of such stimulation will vary, even as the sun rises and sets or as the urinary bladder fills and empties. These cyclic variations and extrinsic stimulation may account in part at least for a diurnal periodicity of sleep. However, one should not forget that experimental animals deprived of the cortex seem to show alternating periods of sleep and wakefulness of a sort, although just what kind of awareness is possible in these animals is difficult to imagine (97).

'Intrinsic' influences acting upon the cortex are derived from subcortical structures. These, of course, are in turn affected by afferent impulses, metabolic changes and other changes of the internal environment. The intrinsic factors are necessary to maintain the wakefulness which is possible at low levels of extrinsic stimulation and must play very important roles indeed; for when the areas of the brain containing these crucial regions are disabled, sleep ensues in spite of normal levels of extrinsic stimulation. Magoun (105) and his co-workers have developed the idea of an activating system in the reticular formation of the brain stem responsible for cortical wakefulness. The role of the reticular system in this matter is discussed in Chapter LII of this work by French. Sleep is considered in Chapter LXIV written by Lindsley.

OTHER DIENCEPHALIC RELATIONSHIPS. Diencephalic and preoptic lesions have been noted to be associated with gastric erosions which approach severe ulceration and also with pulmonary edema. The gastric erosions are a manifestation of a fairly general dis-

turbance of the gastrointestinal tract due to autonomic imbalance (see also Chapter XLV by Eliasson).

The occurrence of pulmonary edema raises a number of questions. It has been found experimentally that preoptic lesions in rats are followed by edema of the lungs, and mid-line lesions dorsal to the chiasm seem to be the most effective (108, 109). This edema is not influenced by vagotomy, but it is prevented by cervical spinal transection or section of the splanchnic nerves. Maire & Patton suggest that the preoptic lung edema results from overloading of the pulmonary circuit owing to splanchnic-mediated constriction of visceral venous reservoirs, since the liver and spleen weights of animals dying from lung edema are significantly less than normal.

The hypothalamus is known to participate in so-called stress reactions. Using eosinopenia as an index, Porter (137) found that the response to epinephrine, formalin and histamine in the cat was prevented by lesions in the posterior part of the hypothalamus but not by anterior hypothalamic lesions. He also found that direct stimulation of the tuberal and mammillary areas produced eosinopenia. Presumably these effects are mediated through the anterior lobe of the pituitary. Mirsky *et al.* (120) found that noxious stimulation brought about increased production of antidiuretic hormone in rats. This was also true after hypophysectomy; presumably the sources of the antidiuretic hormone were the neurons of the supraoptic nucleus. Mirsky suggests that possibly the antidiuretic hormone may participate in the neurohumoral activation of the anterior lobe [cf. Martini *et al.* (111); Chapters XXXIX and XL of this work]. McCann & Sydnor (112) were able to prevent the rise of blood ACTH which ordinarily occurs during stress by lesions which interrupted the supraoptico-hypophysial tract. There may be a question here, however, as to whether the lesions of the supraoptico-hypophysial tract did not also interrupt the hypophysial portal system of veins.

CEREBRAL AND CEREBELLAR AUTONOMIC MECHANISMS

A fairly extensive literature substantiates the participation of the cerebral cortex in autonomic activities. A number of comprehensive reviews are available, including those of Fulton (56) and Kennard (96). Other key references are Pinkston *et al.* (133), Pinkston & Rioch (134) and Hoff (78). The subject is discussed also in Chapters LVI, LVII and LVIII of this work. The observations upon which this literature depends have been made upon patients in the clinic and upon experimental animals. Physicians have long been aware of the fact that following the onset of hemiplegia the paralyzed extremities of a patient show vasodilatation which later subsides as the skin becomes paler and colder and increased sweating appears. There is sometimes increased permeability of the capillaries with resultant edema. Many experimental observations have been recorded but no attempt will be made to summarize them here except in a very general way, bringing into consideration only a few relatively recent observations.

Autonomic effects which may be elicited by stimulation of the nonrhinencephalic cortex seem to be most easily elicited from the frontal lobes, especially from the anterior part of the motor area and extending into areas 6 and 8. From the latter, the frontal eye fields, pupillary changes may be elicited; and it is in connection with the pupil that an exception exists so far as localization is concerned because constriction can be produced in cats by stimulation in the occipital region. Vascular changes in response to cortical stimulation of the neopallium most commonly result in increase in arterial pressure, and lesions of the same areas in animals tend to produce a chronic vasodilatation. However, Uvnäs (103) and his collaborators have presented evidence for a sympathetic vasodilator outflow originating in the motor cortex of the dog, with relays in the hypothalamus and midbrain. Uvnäs discusses this system in detail in Chapter XLIV of this work.

Changes in activity of the sweat glands may also be produced by stimulation of the motor areas in animals, as indicated by the galvanic skin reflex of the contralateral side. Increased sweating may appear contralateral to lesions of the frontal lobe, while a persistent piloerection may follow bilateral removal of area 6 (96). Extensive bilateral lesions in the paracentral lobule result in loss of bladder control. Respiratory changes are most readily obtained by stimulation of the orbitofrontal cortex, and psychic influences on respiration as well as on salivation and other autonomic phenomena are well-known.

Generally speaking, there is a fair amount of discrete localization of autonomic areas in the motor and premotor regions, usually in fairly close relation to corresponding somatic representations. Kennard suggests that such control as may exist from these areas is that of regulation of finer autonomic adjustments; when this control is lost, there is loss of inhibition and there may be, as a result, overreactivity. Recently, autonomic effects from other regions of the cortex

have been found by Hoffman & Rasmussen (80). Stimulation of the insular cortex in the monkey produced a fall in arterial pressure, inhibition of respiration in expiration, decrease in tonus of the stomach and inhibition of gastric peristalsis, the two latter being eliminated by section of the vagi. Stimulation of the insular region in man also gives some indication that this area is concerned with visceral functions (131, 132).

It has already been mentioned that the cortex has extensive fiber connections, mostly indirect, with the hypothalamus and lower regions of the brain stem. An extensive discussion of these connections is to be found in Mitchell (121), although some of the evidence cited has not been substantiated (9). However, the functional connections are rich, and Rossi & Brodal (141) have found corticofugal fibers passing from the cortex to the reticular formation of the pons and medulla, with the motor area as the chief contributor. These fibers, descending in the pyramidal tract, provide a nonhypothalamic route for influencing somatomotor and autonomic functions.

The question arises as to what extent autonomic responses evoked from the cerebral cortex are mediated through the hypothalamus. Landau (100) approached this problem by stimulation of the corticospinal tract in the medulla, producing sweating, changes in arterial pressure and pulse rate, contraction of the bladder and of the stomach, pupillary changes, and piloerection. In his opinion the cortex can influence most autonomic functions by way of the spinal cord, separately from the hypothalamus and its pathways, and he proposes the predominant effect on visceral function to be one of facilitation of activity patterns which are essentially determined at spinal and peripheral levels. Wall & Davis (165), by exciting the cortex after removal of surface afferents by section of the trigeminal nerves, found that stimulation of the sensorimotor cortex, the anterior part of the gyrus cinguli, the posterior orbital cortex, the anterior part of the insula and the anterior part of the temporal lobe produced arterial pressure changes. Responses elicited from the sensorimotor area were independent of the hypothalamus and could be abolished by section of the pyramid. They also observed that the temporal lobe responses did not depend upon the hypothalamus. Responses produced by stimulation of the posterior orbital cortex and the insula were abolished by destruction of the hypothalamus; however, some respiratory responses remained.

Some other interesting observations have recently been presented by Hoff *et al.* (79) who found that stimulation of the anterior sigmoid gyrus in cats causes an elevated arterial pressure plus a renal cortical ischemia, the latter being prevented by renal denervation. Upon repeated stimulation, fatty degeneration and, later, lower nephron nephrosis occurs due to chronic vasoconstriction. On the other hand, Johnson & Browne (90) found that ablation of autonomic cortical zones had no effect on the arterial pressure in dogs with chronic renal hypertension, the reason probably being the multiplicity of cortical areas concerned with vasomotor functions.

The influence of cortical extirpation upon emotional responses has already been mentioned, but this is no place for an extensive discussion of this topic which is the subject of Chapters LXIII and LXIX. It will be recalled, however, that decortication in animals has been said to lower the threshold for rage; and since rage phenomena are closely associated with outbursts of autonomic activity, this relationship becomes of interest. However, Rothfield & Harman (142) found that such a lowering of the rage threshold by decortication was dependent upon concomitant interruption of the fornix and postulated that inhibitory influences pass from the rhinencephalon to the hypothalamic 'rage integrating center' via the fornix. If confirmed, this will add support to the Papez theory of the anatomical basis for emotions.

A great deal of detailed work has been done recently concerning the activities of the rhinencephalic areas, including the amygdala and piriform lobe, hippocampus, gyrus cinguli and subcallosal regions. The functions of these areas will be thoroughly discussed in Chapters LVI, LVII and LVIII of this work, and it is sufficient to state here that these areas have important relationships to autonomic function, some of which may be carried out in collaboration with the hypothalamus, as has already been mentioned. Some similarity of the effects of lesions in the amygdaloid nuclei and lesions in the hypothalamus has been claimed. For instance, Morgane & Kosman (124) have reported that hyperphagia follows bilateral amygdaloidectomy in cats, a finding in variance with that of Anand & Brobeck (5) who found no change in food intake but simply decreased activity. There is a possibility that rhinencephalic structures may be intermediary in the activation of the anterior hypophysis through the hypothalamic route. Sawyer (146) found that the release of pituitary gonadotrophin produced by intraventricularly injected histamine in rabbits is probably due to excitation of rhinencephalic pathways and not to direct action on the adenohypophysis.

The rhinencephalic structures act in turn upon the neurosecretory mechanisms of the hypothalamus.

In the past it has frequently been proposed that the cerebellum participates in autonomic activities, but most of these suggestions were not substantiated by adequate evidence. For instance, in cases of stimulation of the cerebellum it was not at the time possible to guard against spread of current to adjacent medullary and pontine mechanisms. The first work which demonstrated with any authority that the cerebellum may have an effect on autonomic functions was reported by Moruzzi, starting in 1938 and summarized more recently (125). Using cats with the brain stem transected at the precollicular level, Moruzzi was able to demonstrate inhibition of both vasoconstrictor and vasodilator reflexes. The same was also true for the increased vasoconstrictor and respiratory activity produced by ligation of the common carotid arteries. Moruzzi also stimulated the cerebellum during fits of sham rage. Here a remarkable effect, presumably upon the hypothalamus, was produced, since the somatic and autonomic manifestations of the sham rage were immediately inhibited. After cessation of the stimulation, a characteristic cerebellar type of rebound manifestation was seen in that the somatic and autonomic characteristics of the sham rage reappeared. Moruzzi also observed diphasic pupillary responses upon cerebellar stimulation in which a parasympathetic miotic effect during stimulation was followed by a sympathetic mydriatic response during the rebound period. To quote, "Apparently the cerebellum, or at least its median structures, can play upon many central functions besides postural tonus, but the diphasic response to an electrical stimulation seems to be a permanent feature of all cerebellar effects, as if the cerebellum were mainly concerned with sending a sequence of inhibitory and facilitating volleys to the brain stem neurons, the type of the response depending upon the structure to which the cerebellar impulses arrive" (125).

More recently, Zanchetti & Zoccolini (177) stimulated the fastigial nuclei of the cerebellum in acute thalamic cats. Such stimulation caused outbursts of the sham rage type, including autonomic effects. These were also produced by stimulation of the midline structures and from the buried folia of the tuber, pyramid and uvula. Diencephalic centers were necessary for these responses, since they were abolished by rostral midbrain coagulation. Ban and his co-workers (11) studied cerebellohypothalamic relationships as revealed by electrical recording methods. There was a marked increase in the frequency and voltage of the EEG of the ventromedial hypothalamic nucleus, together with sympathetic manifestations, when the anterior lobe of the cerebellum was stimulated. That of the lateral hypothalamic nucleus showed slight increases in frequency. In the reverse direction, the EEG of the anterior lobe of the cerebellum was also increased in frequency and voltage by stimulation of the ventromedial hypothalamic nucleus. Peripheral autonomic responses produced by stimulation of the lateral hypothalamic area were prevented by stimulation of the cerebellar anterior lobe. The authors postulate that the cerebellum not only modulates autonomic activity at the level of the lower brain stem but also may modulate the autonomic activities of the hypothalamus.

One of the more striking evidences of cerebellar participation in autonomic reflexes is presented by the work of Bard *et al.* (15) who demonstrated that motion sickness in dogs is prevented by excision of the flocculonodular lobe of the cerebellum.

CONCLUSION

Central autonomic mechanisms exhibit a crescendo of complexities. In the isolated spinal cord many of the autonomic mechanisms are truly capable of autonomous activity. These reflexes resemble somatic reflex circuits in many ways, and are capable of analysis as to their synaptic relationships and reflex times. They appear, under normal circumstances, to be subject to facilitatory and inhibitory influences from higher areas, and here some restriction of their autonomous status appears. There is also good evidence that these spinal circuits may be capable of projecting to the higher regions, even as high as the cerebral cortex, over definite afferent pathways by which they may bring the modulating feed-back influence of the higher regions into action. Separated from the higher brain, these segmental mechanisms function only for the needs of the moment. They are largely incapable of functioning in the broad sense of maintaining the homeostasis and homeokinesis of the body after the influence of the brain has been removed by spinal transection.

As we go on to the lower brain-stem complexes, again we find circuits of different types so arranged as to make feed-back and reverberation possible, making use of the innumerable internuncial neurons of the reticular formation for elaborating patterns of control

of spinal autonomic activities. The focal points of a number of these patterns of control seem to be highly localized in the medulla oblongata. Here we can spot them chiefly by picking up the points of efferent flow. It has already been argued that the ordinary concept of neural 'center' is hardly adequate for the consideration of these neural patterns, which may be extensive. These brain-stem autonomic circuits must also have the capacity for feeding to the diencephalon and cortex and of bringing into play at these higher levels still further patterns of integration, which in turn may feed back into the brain stem and cord.

Interactions between the somatic and autonomic mechanisms must not be overlooked. It has been clearly shown that these interactions are not only present but exceedingly important. Changes in the environment which affect initially the soma can be brought into close relationship with autonomic responses as well. These somatovisceral and viscerosomatic circuits are also modulated by influences from higher regions. This modulation may be tonic or it may be brought into play by ascending impulses arising in these circuits.

The midbrain contains relatively few of the more spectacular autonomic mechanisms, but through this region a flood of ascending and descending impulses pass, including those picked up by the reticular formation from the great afferent pathways and passed on in some fashion to activate and otherwise modify the activities of the cerebral cortex. Here also we have a set-up for chemical modulation; just as in the medulla we find the activities of the respiratory and other centers modified by changes in the blood, in the midbrain also we may find important effects by certain hormones, such as epinephrine, through which the complicated neural discharges characteristic of emotional responses may be reinforced and prolonged.

In the diencephalon, autonomic functions are centered largely in the hypothalamus which is intimately related to the reticular formation of the brain stem. Here again we have focal areas, as in the medulla, which can be artificially aroused to activity by direct stimulation under laboratory conditions or which can be destroyed and thus modify the total picture of autonomic activity. This small region seems to be a crossroads for complicated circuits subserving patterns of behavior, many of which appear to be primitive; but also we have an organization capable of inhibiting primitive reaction patterns, for example savageness and rage. While the hypothalamus is necessary for the maximum expression of rage, it also normally contains some sort of arrangement which makes it possible for the domestic animal to react more favorably to his fellow animals. This is evidently true for man as well as for the carnivore or ungulate.

The thalamus participates in this type of activity, chiefly because it provides means of communication between cerebral structures and the hypothalamus and lower brain stem. The interactions of the cerebral cortex and the thalamus in the integration of sensation have received much consideration from clinicians and physiologists, and newer findings on the rhinencephalic or limbic portions of the hemisphere and their participation in autonomic activities offer great promise for advances, not only in the partial elucidation of problems of emotional behavior but of the regulation of the internal milieu of the organism. It is evident that the farther we go and the more we study, the more interactions are uncovered, for everything which has been said in this chapter argues against the concept that any portion of the brain serves as an isolated structural or functional entity.

Specific participation of the sympathetic and parasympathetic divisions of the autonomic or vegetative division of the nervous system in these processes has received little emphasis in the foregoing paragraphs. They nevertheless emphasize the fact that all levels of the nervous system have a similar basic organization. The concept of levels is valid only because it expresses increasing potentialities for interaction and integration. As one passes from the spinal cord through the brain, the addition of increasing numbers of neurons brings increasing possibilities for, and probabilities of, interaction. Physiologically and anatomically, we are beginning to have glimmerings of the basic types of fundamental neural circuits. However, who knows but what the concepts of 'circuits,' of 'feed-back' and of 'reverberation' may one day seem to contemporary scientists as ridiculous as the humoral theory of disease does to us. The latter theory, however, marked a great advance in medical and biological science, sufficient unto its day. One can perhaps look forward to the time when the interactions of peripheral ganglia, spinal cord, medulla, pons, midbrain, diencephalon, cerebellum and telencephalon will present to the scientist a unified and not altogether incomprehensible picture, not constituted of segmental moieties or theories of emotion or of the laws of learning, but a system in which the vegetative, the somatic and the psychic may be blended in their true proportions. It will not be a simple picture.

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Peripheral autonomic mechanisms

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CHAPTER CONTENTS

THE CLASSICAL EXPERIMENTS OF Langley gave strong evidence for the view that the peripheral autonomic nervous system is principally organized as a two-neuron pathway. Nerve cells situated in the central nervous system give rise to fibers, the preganglionic fibers, which run via cranial nerves and ventral roots of the spinal cord to the peripheral autonomic ganglia where they are synaptically connected to nerve cells constituting the second neuron link. The axons emerging from the ganglia, the postganglionic fibers, then give innervation to smooth muscle, heart and glands. This conception of the general organization of the autonomic nervous system is now—although severely criticized by some neurohistologists—generally accepted in physiology.

Mainly on the basis of differences in the action of drugs on the craniosacral and on the thoracolumbar autonomic neuroeffector systems, Langley proposed that these systems should be recognized as two different divisions of the autonomic nervous system. He therefore restricted the name sympathetic to the thoracolumbar division and called the craniosacral division the parasympathetic system.

As evidence accumulated that the autonomic nerve fibers acted on their effector cells by liberating acetylcholine or an epinephrine-like mediator, a classification of the fibers on this physiological basis was indicated. Dale (91) proposed the names cholinergic and adrenergic. The classification of autonomic nerves into sympathetic-parasympathetic and adrenergic-cholinergic is now generally accepted anatomical and physiological nomenclature.

Acetylcholine seems to be the synaptic transmitter in sympathetic (145, 147) as well as in parasympathetic ganglia (133, 340). Accordingly all preganglionic fibers are cholinergic. There is good evidence that the postganglionic parasympathetic fibers also are cholinergic, but exceptions have been claimed to exist (253). In general the sympathetic postganglionic nerves have been shown to be adrenergic, but it has become highly probable that the sudomotor fibers in man and cat (93) and the vasodilators to voluntary muscle in cat and dog (61, 153, 426) are cholinergic. It has also been claimed that a fraction of the sympathetic fibers to the nictitating membrane of the cat are cholinergic (12, 66). A detailed discus-

TABLE 1. *Spinal Cord Segments Giving Rise to Autonomic Outflows*

Species	Thoracolumbar Outflow	Sacral Outflow
Man (341, 385)	T1–L2[L1 or L3]	S3[S2]–S4[S5]
Monkey (385, 387, 449)	T1 or T2 – L3 or L4[L5]	S1 – S2[S3]
Dog (258, 311, 385)	T2[T1] – L4[L5, L6]	S2[S1] – S3
Cat (258, 385)	T1[T2] – L4[L5]	S2[S1] – S3[S2]
Rabbit (258)	T1 – L5	

Figures in parentheses are reference numbers.
Rare variants in brackets.

sion of the autonomic transmitters appears in Chapter VII by von Euler in this work.

GENERAL ORGANIZATION OF PERIPHERAL AUTONOMIC NERVOUS SYSTEM

Sympathetic Division

The preganglionic fibers arise from nerve cells in the intermediolateral column of the thoracic and upper lumbar segments and leave the spinal cord via the ventral roots to run through the white communicating rami to the trunk ganglia or to the prevertebral ganglia. The upper limit of the preganglionic outflow in man and various animals is T1, but the caudal extension is more variable (table 1). Generally the spinal centers for the sympathetic innervation of structures such as the eye, the heart and the blood vessels of the hand are located in two or more segments (table 2). Variations between animals of the same species and asymmetry often exist and the preganglionic outflow can be markedly inconstant, especially in the lumbar region, as shown for the sudomotor and pilomotor fibers to the lower extremities of man (202, 350).

On the basis of anatomical studies, it has been suggested that nerve cells in the intermediomedial part of the spinal cord also give rise to preganglionic fibers which run up into the cervical and down into the lower lumbar region (cf. 317). There is, however, no physiological evidence for an autonomic outflow from these parts of the spinal cord, and the anatomical evidence is of speculative character only.

It has been claimed that autonomic efferent fibers also emerge through the dorsal roots. The evidence is mainly based on the well-known observations of vasodilation mediated by dorsal root fibers (cf. 17, 155) and on the demonstration of intact nerve fibers in the central stump after section of dorsal roots (cf. 384, 448). However, the anatomical evidence has been found to be unreliable as the observed undegenerated fibers may be regenerating axons from the distal stump (209, 398, 438). Moreover, the ratio between the cells in the spinal ganglion and the fibers in the dorsal root seems to be 1:1 (113, 214), and no convincing neurohistological or physiological evidence has been brought forth that there are synaptic structures in these ganglia. The physiological evidence for the existence of efferent dorsal root vasodilators has been severely criticized by several investigators (cf. 152). Recent reinvestigation of the problem by Folkow *et al.* (155) has made the existence of such fibers seem highly improbable.

TABLE 2. *Spinal Cord Segments Providing Sympathetic Innervation to Various Regions*

	Monkey	Dog	Cat
Eye	T1–T4 (166) C8–T3 (320)	T1–T3 (258, 320)	T1–T3 (258) [C8 T1–T2 (320) T1–T4[T5] (166)
Submaxillary gland		T1–T5 (258)	T1–T5 (258)
Heart		T2–T6 (373)	T1–T5 (258) T2–T5 (45, 69)
Bronchi			T1–T4 (105)
Upper extremity	T4–T8 (386)		
Lower extremity	T12–L3 (386)		T11–L4 (386)
Forefoot	T4–T10 (166)		T4[T3]–T9-[T10] (166, 257, 259, 260)
Hind foot	T10–L3 (166)		T12[T11]–L4 (166, 257, 259, 260, 336)

Figures in parentheses are reference numbers.
Rare variants in brackets.

The distribution and anatomical variations of the white and grey rami and their fiber components have been studied by several investigators (96, 311, 341, 385, 387) whose results on the whole confirmed the observations of Langley. The existence of some postganglionic pilomotor fibers in lumbar white rami was already demonstrated by Langley (263). However, some findings of importance for physiological research work have complicated the picture. According to Hare (190) the grey rami in some instances

may contain both pre- and postganglionic fibers and Zuckerman (449) and Sheehan & Pick (341, 387) have shown that mixed rami are not uncommon. Furthermore, it has been shown by Wrete (445–447) and other investigators (5, 341, 351, 392) that there are intermediate ganglia located distally in the grey rami or in the proximal part of the spinal nerves especially in the cervical and lumbar region (cf. 250). Groups of ganglion cells are also distributed along the internal carotid nerves and plexuses (36, 316).

Each preganglionic fiber belonging to the vasomotor and pilomotor systems runs, as shown by Langley (263), either upwards (middle and upper thoracic region) or downwards (lower thoracic and lumbar region) in the sympathetic trunk. Usually each descending fiber makes connections with nerve cells in three (cat) or four (dog) consecutive segmental ganglia, the ascending fibers supplying as a rule a greater number of ganglia. The fibers running to the superior cervical, the stellate and the coccygeal ganglia may, on the other hand, send all their branches to one ganglion. The preganglionic fibers from an entire white ramus have more extensive connections and may activate as many as eight ganglia (265). Pathways for topographically more restricted sudomotor discharge have been demonstrated in the cat by Patton (336).

It is generally assumed that a single preganglionic fiber is connected to postganglionic neurons belonging to one effector system only. Evidence for such an organization has been given for some fiber groups in the cervical sympathetic (see the next section on fiber types). Although the well-known observations of dissociation of, for instance, vasomotor and sudomotor activity in certain skin areas suggest a functional discreteness, on the whole more direct proofs for this assumption do not seem to exist. On the contrary, it has been shown that preganglionic fibers giving collaterals to sudomotor neurons in the upper sacral ganglia may descend to more caudally located ganglia supplying other autonomic effectors (336).

The postganglionic outflow via grey rami to the spinal nerves follows these nerves to the periphery, giving innervation to segmental areas. These sympathetic dermatomes correspond on the whole to the sensory ones (42, 169, 357, 359, 360, 444), but in many instances a great variability exists in overlap and in the area of autonomic innervation of each peripheral nerve (188, 358). Furthermore, the areas of sudomotor and of pilomotor supply from a given ganglionic outflow may not correspond (350).

Parasympathetic Division

The nerve cells giving rise to the cranial parasympathetic are located in the general visceral efferent column in the brain stem, and the preganglionic fibers emerge via the third, seventh, ninth and tenth cranial nerves. There is no general agreement about the exact localization of the cells (167, 304, 319, 408, 409, 430, 432, 433).

The general organization of the parasympathetic components in the third, seventh and ninth cranial nerves is relatively simple compared with the sympathetic system, each component connecting with neurons in only one ganglion from which the postganglionic fibers are generally distributed to locally restricted structures only. In contrast to this, the autonomic efferents of the vagus have a wide distribution and their connections with the intramural ganglia of the thoracic and abdominal viscera are not as yet fully understood.

Analysis of the origin and course of the vagal autonomic efferents has met with several difficulties. One severe obstacle has been that sensory fibers are the dominating component of the vagus, a fact making a quantitative determination of the number of the fine preganglionic fibers difficult. Foley & DuBois (149) showed that only 20 to 35 per cent of the total number of fibers just distal to the jugular ganglion are parasympathetic efferents in the cat. Evans & Murray (136) found that the corresponding values for the rabbit cervical vagus are 20 to 25 per cent and that less than 10 per cent of the vagal fibers entering the abdomen belong to the parasympathetic system. Another obstacle has been that sympathetic fibers join the vagus to a variable degree (cf. 95, 319, 354). In the rabbit, as shown by Evans & Murray, about 5 per cent of the total number (altogether about 26,000) of the fibers going to the abdominal viscera remain intact after cervical vagotomy. They are probably of sympathetic origin, but their destination and function are as yet unknown.

Heinbecker & O'Leary (197) have claimed that there are efferent neurons in the nodose ganglion with both centrally and peripherally directed processes and with motor function for the bronchi and the duodenum. Recent investigations (94, 136) have, however, given both anatomical and physiological evidence that makes the construction of Bishop and O'Leary both unnecessary and impossible to accept.

Although it may thus be regarded as firmly established that the parasympathetic efferents in the vagus nerve all emerge from the central nervous system,

there are other problems as yet unsolved. Langley (268) had already pointed out the peculiarity that relatively few preganglionic fibers were distributed to such large territories as the esophageal and enteric plexuses. It was not fully understood, however, what a discrepancy exists in the proportion between the preganglionic fibers and the postulated postganglionic neurons, until Evans & Murray (136) obtained more reliable quantitative data for the rabbit vagus. Only about 3000 efferent fibers from both vagi together seem to enter the abdominal cavity, that is to say about as many as the preganglionic fibers supplying the ciliary ganglion in the cat (442). This stands in sharp contrast to the number of enteric nerve cells which probably amount to several million (cf. 223, 375).

Several neurohistological studies have clearly shown that preganglionic vagal axons enter the intramural ganglia in the gastrointestinal canal probably making synaptic connections with at least some of the nerve cells (177, 180, 205, 251, 281, 402). It is often claimed that the vagal fibers synapse with only one of the cell types and that the other neurons are some kind of associative elements connected with each other via dendrites and axon collaterals. Even more detailed constructions of the relations between the different elements can be found in papers concerning gastrointestinal innervation (226). However, these statements are based on interpretations of histological structures. Many of the observed structures have not as yet been conclusively shown to have either functional significance or real existence in the living tissues. Others may be accepted as having both attributes but the interpretations concerning their functions cannot be accepted as conclusive without further evidence. (The difficulties inherent in the neurohistological methods are discussed later in the section on autonomic effector junctions.) There does not exist any view, generally accepted in neurohistology, of the general organization of the pre- and postganglionic elements constituting the enteric plexuses. The neurohistological observations show, however, that very complicated arrangements may exist. In physiology it is generally assumed that the vagal preganglionic fibers synapse with enteric neurons which give rise to postganglionic fibers innervating the smooth musculature and digestive glands. It has been suggested that some of the postganglionic neurons may be adrenergic (7, 323) or that they may have an atropine-resistant transmitter of unknown nature (144, 421). No evidence is as yet available that gives any clue to an understanding of the intraganglionic connections. There are reasons to believe, however, that intrinsic nervous mechanisms may play a role in coordinating the more complex movements of the stomach and intestines (see the later section on autonomic activities independent of the central nervous system).

The sacral parasympathetic emerges from cells in the intermedial region of the upper or middle sacral segments (S_1 to S_3 or S_2 to S_4, table 1) and the preganglionic fibers run via the anterior primary division of the corresponding sacral nerves to the pelvic plexuses. They relay in ganglia in the pelvic plexuses or in the intramural ganglia of the bladder and distal colon. As for the vagal parasympathetic system, the connections between the pre- and postganglionic elements and the intrinsic nervous mechanisms are on the whole unexplored.

It has generally been assumed that the pelvic ganglia, except those supplying the internal reproductive organs, belong to the sacral autonomic outflow only. An experimental analysis in the cat employing neurohistological methods (252, 322) has given at least suggestive evidence, however, that not only the pelvic but also the intramural ganglia of the bladder receive some of their preganglionic fibers from the sympathetic division. This may be taken as an illustration of the difficulties and complications met with in investigations of the nervous mechanisms regulating visceral functions.

Many of the essential problems concerning the anatomy and physiology of the autonomic nervous system which are impossible to consider in a brief survey are extensively discussed in recent monographs (251, 317, 318, 439).

The peripheral distribution of an axon from a single postganglionic neuron is but little known. Histological studies (103) show that the postganglionic fibers may branch soon after leaving the ganglia. In view of the fact that relatively few fibers must give innervation to a large number of cells, it is reasonable to assume that a further and probably extensive branching occurs at the periphery so that a single neuron may activate a large number of effector cells. Studies of postganglionic axon reflexes (see the section on activities of the peripheral autonomic nervous system independent of the central nervous system) do indeed give evidence for the existence of a terminal branching axon system supplying several sweat glands within skin areas up to a size of 2 cm. It is of interest that Downman (110) in his study of the distribution of mesenteric vasoconstrictor and inhibitory fibers

along the small intestine observed a vasoconstriction in territories not more than 2 cm in length on stimulation of small mesenteric nerve bundles. He concluded that the innervation area of the terminal ramifications from an individual axon is at the most of this size. This conclusion seems to be valid as it follows from the experiments that no spatial summation effects produced by fibers in adjacent territories are necessary to give an observable vasoconstriction.

As the cholinergic and the adrenergic mediation seem to be inherent properties of two different types of postganglionic neurons, it is improbable that an individual postganglionic fiber might give both a cholinergic innervation to one structure and an adrenergic supply to another. As a matter of fact, there is not even any convincing evidence as yet that a single postganglionic axon does directly activate two anatomically different structures. (The problem of transmitter diffusion is discussed in the later section on the construction and functional organization of the autonomic innervation apparatus.) On the contrary, several observations suggest that functionally and anatomically different effectors within the same organ are subserved by independent and separate fibers (see e.g. 110, 163, 320).

There are only a few studies directly concerned with the question of the innervation of structures supplied bilaterally with autonomic nerves. In experiments on vagal inhibition of the heart, Brown & Eccles (52) showed that there was no refractory period effect on simultaneous stimulation of the right and left vagi. This indicates that the preganglionic fibers from the two sides have no appreciable convergence to the same group of postganglionics. Another approach to this problem was used by Dye (115, 116). He found that previous exhaustion of a given bilaterally innervated structure by a unilateral stimulation did not affect the response obtainable from stimulation of the corresponding nerves from the opposite side and that summation of responses was linear on brief simultaneous stimulation of the pre- and postganglionic nerves from both sides. This clearly supports the conclusion drawn by Brown & Eccles. It is not so obvious that the two groups of postganglionic neurons, each activated by preganglionic fibers from one side only, distribute their axons to different effector cells within the same anatomical structure, a view championed by Dye. Unfortunately, however, his interpretation is based on assumptions concerning the local production and the local and remote effects of the liberated chemical mediator which are not necessarily valid. As regards the bladder it has been clearly shown by Langley & Anderson (270) that the pelvic nerve supply is strictly unilateral. This has been confirmed by recording the tonic activity in the postganglionic fibers (140).

TABLE 3. *Number and Extent of Myelination of Preganglionic Fibers in the Cervical Sympathetic Trunk of Various Species*

	Total Numbers of Fibers	Proportion of Unmyelinated Fibers
Dog	5400–12800	42–66%
	M = 9900	M = 55%
Cat	5400–10100	1–61%
	M = 7400	M = 37%
Rabbit	1000–3100	
	M = 2100	M = 60%
Rat	2500–3900	98–99%
	M = 3000	

FIBER TYPES AND THEIR FUNCTIONAL SIGNIFICANCE

Gaskell (159) stated that the fibers going to the autonomic ganglia are medullated (1.8 to 3.6 μ) and that the fibers leaving the ganglia are nonmedullated and of very fine caliber. This classical rule was shown, especially by Langley (cf. 267), to have a vast number of exceptions. Since then it has been found that there are not only great differences between animals of different species but also that there are very great variations between animals of the same species (table 3).

In mammals all peripheral autonomic fibers are either small medullated (1 to 3.5 μ and occasionally up to 5 μ) or small nonmedullated (up to 2 μ). As yet no differences in morphology (size and myelination) or in neurophysiological properties (conduction velocity, etc.) have been shown to exist between the sympathetic and the parasympathetic system or between adrenergic and cholinergic fibers.

Quantitative data concerning the number and size of the autonomic fibers in the ventral roots in several mammals and in man have been given, especially by Häggqvist and his associates (cf. 356). Caliber spectra of the ventral roots show that the medullated fibers belonging to the thoracolumbar and sacral autonomic outflows give rise to a separate thin-fiber group (1 to 4 μ) showing a high and distinct peak at 2 to 3 μ and constituting 60 to 75 per cent of the total number of medullated fibers (356). The size of the small medullated fibers in these outflows does not vary to any appreciable extent in cat,

dog, monkey and man, as shown by Sheehan (385). In the white communicating rami of cat, dog and rhesus monkey, Rexed (356) found that the great majority of the myelinated fibers had a size of 1 to 3.5 μ. The same values were reported by Ranson & Billingsley (353) for the cat. Unfortunately there are no reliable quantitative data concerning the number and size of the nonmedullated preganglionic fibers in the ventral roots or white rami. According to Duncan (112) up to 30 to 40 per cent of the fibers in the thoracic ventral roots of the rat may be unmyelinated whereas the number is considerably less in the cat.

Table 3 illustrates the high variability in myelination of the preganglionic fibers in the cervical sympathetic trunk. Data concerning the number, size and myelination of the vagal autonomic efferents have been given (94, 136, 149, 319).

The postganglionic fibers of the grey communicating rami in the cat, dog, monkey and man are predominantly nonmedullated, but some small medullated ones are found to a variable degree (261, 341, 356, 387). Many of the postganglionic fibers from the superior cervical ganglion in the cat (23, 25, 352) and rhesus monkey (25) are medullated; in the rabbit, fewer are present (25). It may be stated that the postganglionic fibers in mammals are for the most part generally of the nonmedullated variety. An interesting exception has been found in the short ciliary nerves which in the cat are of the thin myelinated type (86, 160). The myelin sheaths seem to make their appearance at a considerably later stage of development in autonomic than in somatic nerve fibers (378).

Caliber spectra of peripheral nerves show that the fibers in a given nerve may be divided into separate and often distinct size groups. Since the first experiments by Erlanger and Gasser, evidence has accumulated showing that the groups obtained on the basis of fiber size may correspond to fiber groups with different functions and with different neurophysiological properties. In many instances, however, a given caliber group contains several functionally different fiber groups and fibers with the same function may be distributed to more than one caliber group. That the autonomic fibers can be divided into groups each subserving a particular function has been shown in some instances (see below). It must be stressed, however, that there is as yet no anatomical basis for a division either of the preganglionic or of the postganglionic fibers into more than two groups according to size and to other morphological characteristics. Although there may exist different, more or less distinct size groups, as indicated by neurophysiological studies, caliber spectra of the medullated fibers have not revealed them, and no quantitative data at all concerning the size of the nonmedullated fibers have been given.

An example may illustrate the view expressed above. In a recent work (103) the medullated fibers in the cervical sympathetic trunk of the cat have been divided into three subdivisions: *a)* 6.5 to 5 μ (about 200 fibers), *b)* 4.5 to 3 μ (about 2000) and *c)* 2.5 to 1.5 μ (about 2000). The groups obtained were assumed to correspond to the S_1, S_2 and S_4 fibers of Eccles (see below). It is clear, however, that the preganglionic medullated fibers justifiably may equally be separated into two, five or more subdivisions, a fact which makes the construction unacceptable.

There are other difficulties when an attempt is made to correlate anatomical and functional groups in the autonomic nervous system. Thus, for instance, it was claimed by Langley (258) that many medullated preganglionic fibers lose their myelin sheaths before entering the ganglia. Another obstacle is the very great variability in myelination between animals of the same species, making it almost impossible, as pointed out by Ranson (23) among others, to take the presence or absence of myelin as a criterion for a differentiation of functional types of fibers.

On the basis of neurophysiological properties, the peripheral autonomic fibers may be divided into two principal groups corresponding to the B and C types in the classification of Erlanger and Gasser. It is beyond doubt that in mammals the slow conducting C component is represented by unmedullated fibers only and there is good evidence that the B fibers are medullated ones of the variety found in the autonomic nervous system (cf. 24, 108, 134, 183, 192, 193, 195). The autonomic nonmedullated fibers have physiological properties distinctly different from those of the C fibers arising from dorsal root ganglia (161), but the significance of this is not known.

The C component has not as yet been divided into more distinct subdivisions, although it is clear that this group must in many instances contain fibers going to very different effectors. A composite C wave may be observed in the postganglionic nerves from the superior cervical and ciliary ganglion in the cat (117, 440), but no clearly separable subgroups have been recorded. This applies also to the postganglionic nerves from the superior cervical ganglion of the rabbit (25, 109), from the stellate ganglion of the cat (45, 49, 123), and from the inferior mesenteric

ganglion of the rabbit and the cat (54, 293) where the C type is the main or only component.

The B group, on the other hand, consists in many instances of several components which often overlap concerning conduction velocity but which are more or less distinctly separable on the basis of other properties (threshold, synaptic delay, distribution of fibers, etc.). This has most clearly been shown for the cervical sympathetic in the cat. Bishop & Heinbecker (25) recorded in the preganglionic stretch four spike potential waves, M_1 to M_3 and U, the first three having properties of the B type and the last arising from C fibers. This was confirmed by Eccles (117–119, 121) who made an extensive analysis of the properties of the four fiber groups, labeled S_1 to S_4. The conduction velocities were observed to be approximately 18 to 26, 10 to 12, 7 to 10 and 1.3 to 5 m per sec. The four preganglionic groups were further shown to make synaptic connections with ganglion cells giving rise to four postganglionic fiber groups with considerably slower velocities (approx. 5 to 8, 1.7 to 5 and 1 m per sec.). The postganglionic S_1, probably produced by the medullated fibers found in the cat, was distributed to the eye, S_2 to S_4 were found in all postganglionic branches. The S_2 wave was always the largest. It was assumed by Eccles that the S_1 to S_3 groups in the cervical trunk correspond to medullated fibers presumably of descending order of size and the S_4 to nonmedullated fibers. In some instances with long conduction paths available, S_1 was found to separate out in subsidiary waves, indicating a composite nature. Rosenblueth & Simeone (371) have reported similar findings concerning fiber groups in the cervical sympathetic.

It does not seem unlikely that the four fiber groups present in the cervical sympathetic trunk of the cat and also found in the rabbit and rhesus monkey (25) subserve different functions. In fact, Bishop & Heinbecker (25) have made observations supporting this view. According to them the M_1 fibers activate the sphincter of the pupil, the nictitating membrane and the muscles of Müller; the M_2 group gives vasoconstrictors to the ear and conjunctiva and pilomotors to the hairs between ear and eye. Further evidence was given by Eccles (117) and Brown (51) supporting the view that the preganglionic and postganglionic fibers of highest conduction velocity and of lowest threshold (cat) are distributed to the orbit. The functions of the other groups have not been studied. However, no effects are observed on stimulation of the postganglionic fibers in the rabbit until fibers of the C type are activated (25).

By using other autonomic nerves Bishop & Heinbecker have tried to provide further evidence for the assumption that there exists a correlation between functional fiber groups and groups obtained on a neurophysiological and anatomical basis. In a study of the vagal efferents to the heart of the turtle, Heinbecker (194) claimed that myelinated axons primarily influence an inotropic mechanism whereas chronotropic effects are produced by nonmyelinated fibers. In a later paper (196), however, it was reported that the fibers responsible for both the inotropic and the chronotropic effects belong to both B and C types.

In the cat and monkey Sheehan & Marrazzi (386) have recorded large C waves (with conduction velocity of 1 to 2m per sec.) and small B waves (8 to 20 m per sec.) from peripheral nerves to the limbs on stimulation of ventral roots. Both waves were shown to originate from sympathetic postganglionic fibers. It is not known, however, whether the B fibers have as their destination effectors functionally different from those supplied by the C group.

It may thus be concluded that attempts, on the basis of morphological characteristics, to divide the peripheral autonomic fibers into separate groups other than the two groups based on the presence or absence of myelin and corresponding to B and C fibers have so far been unsuccessful but that the medullated B fibers can in some instances be subdivided on the basis of neurophysiological properties into two or three distinct types. From the studies referred to above it may further be concluded that, with one or two exceptions, there is no experimental evidence which makes it possible to correlate functionally different types of fibers with fiber groups demonstrable by morphological or neurophysiological methods.

In contrast to somatic nerve fibers, the autonomic B and above all C fibers have considerably increased oxygen uptake at low frequency activity and high susceptibility to lack of glucose (277).

STRUCTURE OF AUTONOMIC GANGLIA

Types of Ganglion Cells

No obvious morphological differences have been found between the nerve cells in sympathetic and in parasympathetic ganglia. Although uni- and bipolar cells are sometimes observed, it is evident that the great majority of the postganglionic neurons are multipolar. Great variations in their morphology

exist and many attempts have been made to divide them into certain main types. However, the question may be raised whether the type divisions described have any real meaning.

With the arrangement of the Nissl granules as a criterion the ganglion cells have been divided into two to nine classes (213, 218, 219, 342). The possibility of such a classification has been denied by others (78, 374); but, even if this possibility exists, certainly no evidence has been given to show that the cell types obtained differ from each other from a functional point of view.

Another classification has been made on the basis of size. In analogy to studies of the size of somatic nerve fibers and its relation to fiber properties, this approach may be assumed to give valuable information. Unfortunately, however, no conclusive quantitative data are available. The most extensive studies have been made by de Castro (98, 103) who claims the existence of three size groups which are present in varying proportions in different ganglia. According to him the cells may be classified as large (35 to 55 μ), medium sized (25 to 32 μ) and small (15 to 22 μ). The three groups are represented in the superior cervical ganglion of man by 27, 50 and 23 per cent, the corresponding values for the stellate ganglion being 17, 67 and 16 per cent. The classification is interesting from the point of view that it might give an anatomical basis to the three main, well delimited cell pools found by Eccles (see below). It is obvious, however, that de Castro's classification is open to criticism. The class limits are arbitrary and no analysis of the size-frequency curve has been made to show that three different size types really exist and that the cells are not distributed along a more or less normal frequency curve with one peak only. The work of de Castro indicates, however, that there may be real differences between various ganglia. The cervical ganglia and to a lesser degree the thoracolumbar ganglia have a relatively high proportion of large and small nerve cells in contrast to the prevertebral ganglia which have practically no cells of such a size and therefore show a more uniform picture. This has been found to hold good for several mammals and might obviously be of significance to neurophysiological work as there is evidence that fiber size is correlated with the size of the nerve cells (cf. 356).

The most commonly used classification is based on the morphological appearance of the dendrites. The types I (many short dendrites) and II (varying numbers of long dendrites) of Dogiel have generally been adopted to differentiate the ganglion cells into two main groups assumed to represent two cell types clearly differentiated from each other (cf. 177, 180, 403). Great variations and many cells belonging to neither group have been observed, however (98, 403). The most representative view is that the nerve cells in the autonomic ganglia (the enteric plexuses excluded) of various mammals have predominantly a large number of long processes, often branching extensively, and that only a small number have short, intra- or extracapsular dendrites (98, 103, 248, 249, 352, 403). The ciliary ganglion and maybe other cranial parasympathetic ganglia are exceptions in so far as they seem to have numerous type I cells (98, 103, 343). Mainly on the basis of the morphology and arrangement of the dendrites, de Castro (98, 103) claims the existence of five cell types. There is not as yet more direct evidence concerning the functions of the different ganglion cells.

A new and interesting approach with ganglion-stimulating and ganglion-blocking agents has been used by Shaw and his associates (381–383). Their experiments show that the cells in sympathetic ganglia are not a homogeneous population from a pharmacological point of view and give some support to the hypothesis of Bishop and Heinbecker that distinct cell groups exist in the ganglia, each subserving a particular function.

Connections Between Preganglionic and Postganglionic Neurons

That there may be many more nerve cells in an autonomic ganglion than the preganglionic fibers supplying it was shown by Billingsley & Ranson (22) who found the ratio of myelinated fibers to cells to be 1:32 in the superior cervical ganglion of the cat. Wolf (442), including unmyelinated fibers in the counts, found in two cats a ratio of 1:11 and 1:17. In contrast to this, the ratio for the cat ciliary ganglion is approximately 1:2 (442). The obvious difference between the two ganglia has often been taken as evidence for a more diffuse distribution of the sympathetic system. As no systematic studies comparing ganglia belonging to the two divisions have been made, however, there is no basis for such a generalization. As a matter of fact, observations made by Harris (191) suggest the existence of a 1:2 ratio in the inferior mesenteric ganglia of the cat.

It may be concluded from the studies referred to above that in many instances several or even numerous ganglion cells are supplied by individual pre-

ganglionic axons. This conclusion is based on the postulate of Langley that the preganglionic fibers make synaptic connections directly with the postganglionic neurons. The validity of this postulate is discussed below.

As the morphological construction and the localization of the synaptic structures in autonomic ganglia are of importance to an understanding of the internal ganglion organization, some critical comments may be necessary. It must be stressed, however, that no generally accepted view exists concerning the structure of the ganglionic synapse and that the various neurohistological schools have given very divergent interpretations. This unfortunate state of affairs has two principal causes. On the one hand, there are very great difficulties inherent in the neurohistological methods commonly used which often make it impossible to decide whether a microscopically demonstrable structure is of a nervous nature or not. Frequently there is not even any evidence that the observed structures are structures really existing in the living tissue. On the other hand, in spite of these difficulties, there is a general tendency in neurohistology to ascribe synaptic functions to various histological structures without rigid criteria or without any evidence at all for such an interpretation. The facts and reasons on which this critical view is based are discussed in a study of the ganglionic synapse (206). The neurohistological work of the last decade has not revealed any new evidence concerning the methodological difficulties in neurohistology as may be seen from recent investigations (33, 84, 103, 179, 226, 242, 405).

The earlier investigations into the morphology of the ganglionic synapse have been reviewed in several papers (26, 206, 329, 403). Recent studies have not revealed any new aspects of the picture (see e.g. 103, 179, 226, 242).

The structures most commonly described as synaptic are small ring or club-like endings or reticulated enlargements in the vicinity of cell body or dendrites (103, 168, 226, 242, 244, 245) and different types of pericellular arborizations or arborizations in dendritic tracts and glomeruli (103, 248, 249). Silver impregnation techniques, as their defenders admit (e.g. 103, 226), reveal structures assumed to be real preganglionic endings only with great difficulty. Whether these structures, found very sparsely in autonomic ganglia, are more than fragments of terminal axon ramifications may be questioned (cf. 206). The school of Stöhr (355, 404) denies the existence of such free nerve endings and believes the pre-postganglionic junction to be a syncytial asynaptic structure with a terminal reticulum.

Intravital staining of autonomic ganglia with methylene blue by Hillarp (206) consistently revealed a dense plexus of very fine nerve fibers directly on the surface of the ganglion cells, enclosing them. The plexus is formed by the terminal ramifications of one or more preganglionic axons. The fact that the impulse-transmitting ability of a ganglion reappears after nerve section when this intracapsular pericellular structure regenerates is strong evidence that it is synaptic. No such evidence has been adduced for the other structures claimed to have synaptic function. However, it cannot be assumed that the pericellular apparatus of Hillarp is the only form of synapse in autonomic ganglia. The dendrites possessed by certain postganglionic neurons may well make synaptic connections.

The nerve fibers enclosing the cell body of autonomic ganglion cells have recently been observed by electron microscopy, and the pre- and postsynaptic elements have been shown to possess a membrane 70 to 100 Å thick, separated from each other by a space 100 to 150 Å wide (79, 104).

Interneurons with processes wholly confined within a ganglion and synaptic connections between postganglionic neurons via axon collaterals have been claimed to exist by neurohistologists (107, 215, 278, 343) but denied by others (233, 234, 266, 374). No pericellular synaptic structures were observed in the superior cervical ganglion of rats after preganglionic denervation (206). The histological evidence for the existence of such connectional elements is inconclusive, and the many neurophysiological studies made on autonomic ganglia have failed to reveal neurons of this nature.

Many different arrangements of the short and long processes emerging from the postganglionic cell bodies have been described (see 98, 103). Although a clear differentiation between axons and dendrites is difficult and often impossible (177, 178), the processes are usually assumed to be dendrites. Stöhr with his extensive experience in the neurohistology of autonomic ganglia denies the possibility of such a distinction (403). Although many interpretations of the functional significance of the neuronal processes have been presented, it may be questioned whether the neurohistological observations as yet permit any statement to be made. The presence of an extensive system of cell processes indicates the possibility, however, that the autonomic ganglia may have a more complicated construction than was postulated by Langley.

The classic work of Langley led to the conclusion that the autonomic ganglia act solely or mainly as relay or distribution stations in the peripheral pathways. Querido (348) seems to have been the first to question this view seriously on an experimental basis, suggesting that a ganglion has the ability to transform the ingoing impulses to an optimal frequency. From a comparison of the contractions of the nictitating membrane on pre- and on postganglionic stimulation, strong, although indirect, evidence was obtained that the superior cervical ganglion does not alter the frequency of the incident impulses (51, 247, 420).

More direct results concerning the functions of the autonomic ganglia were obtained with the new neurophysiological methods introduced in the early thirties. At maximal preganglionic stimulation each preganglionic volley gives rise to a maximal postganglionic volley, the discharge rate being the same as the stimulation frequency (25, 117, 118). It was also observed that no after-discharge occurs until the stimulation frequency is well above the upper limit of the physiological discharge rate (47–49, 123, 275). Observations on the discharge of individual postganglionic neurons confirmed the results obtained from the studies of whole ganglia or large ganglion cell groups (44, 47, 49, 276). This one-to-one relationship between ingoing and outcoming impulses was the first discovery of fundamental importance for the relay hypothesis.

In the basic works of Bishop & Heinbecker (25) and especially of Eccles (117, 118), it was demonstrated that each of the preganglionic fiber groups (S_1 to S_4 according to Eccles) to the superior cervical ganglion in the cat makes synaptic connections with a particular ganglion cell pool without any appreciable overlap, thus showing the existence of four different cell groups not connected with each other. This was on the whole confirmed by Rosenblueth & Simeone (371), but they concluded that the S_4 cell group may to some extent be supplied also by S_1 and S_2 fibers. In other ganglia no such high degree of differentiation has been found (cf. 273, 293, 294, 330, 440).

Of greater importance for our understanding of the ganglion construction were the observations of Eccles (118, 119). He showed that there is a convergence of several preganglionic fibers on to each ganglion cell in the S_1 and S_2 cell pools and that a single impulse in a single preganglionic fiber excites the ganglion cells supplied by the fiber subliminally only, simultaneous impulses arriving from other fibers being necessary to set up a discharge. The convergence principle has been found to hold good for the inferior mesenteric ganglia (293, 294, 310) and the stellate ganglion (276). In the latter ganglion Job & Lundberg (232) showed that an occlusion of more than 70 per cent may be observed between the ganglion cell pools excited by fibers from the third white ramus and from lower segments. In the ciliary ganglion, however, no overlap between different preganglionic pathways to the main ganglion cell groups could be demonstrated but seems to exist within a minor group (440). As in the S_1 and S_2 cell pools of the superior cervical ganglion an appreciable subliminal fringe has been observed in the stellate ganglion (276), but contrary to this the cells in the inferior mesenteric (293, 294) and in the ciliary ganglion (440) receive enough synaptic endings from an individual preganglionic fiber to be supraliminally excited. Another important finding was that ganglion cells subliminally excited by a single impulse could be brought to discharge by trains of impulses (44, 118, 121, 276).

The demonstration of overlap, subliminal fringe and occlusion, and of the possibility of spatial and temporal summation within autonomic ganglia clearly indicates that the ganglia may have activities and organization like those found in the central nervous system. The basic evidence for the relay hypothesis, the one-to-one relationship between ingoing and outgoing impulses and the nonexistence of after-discharge, may thus be inconclusive in part at least. As pointed out by Bronk (44) there is a more or less rhythmic bombardment of the ganglion cells by impulses from the autonomic centers, and impulses of varying frequency may arrive at a postganglionic neuron from several preganglionic fibers. This makes it possible for the demonstrated mechanisms to come into action and a ganglion may thus modify the incident impulses and show coordinating activities. The demonstration of short- and long-lasting states of facilitation and inhibition in the synaptic terminals and the postganglionic neurons (120, 122, 124, 232, 274, 296) further accentuates the possible existence of such activities. Unfortunately, however, there is no evidence directly showing how the presumed integrative activities work and in what way they modify the impulses from the autonomic centers and what significance they have for the regulation of different effectors. That a group of ganglion cells may be connected to separate sets of preganglionic fibers emerging from different spinal segments presumably makes it possible for different afferent reflex mechanisms to control a particular effector, but this does not give any clue to the other problems. That integrative

mechanisms within autonomic ganglia do not give large and easily detectable effects may be inferred from the fact that the characteristically grouped discharges from the cardiac sympathetic centers are not altered in their form and frequency by passing through the stellate ganglion (45).

The old problem of the role played by the short and long cell processes assumed to be dendrites in the autonomic ganglia has not as yet been elucidated in neurophysiological studies. The evidence brought forth by Lorente de Nó & Laporte (296), indicating that the presynaptic fibers exert excitatory and inhibitory actions on different parts of the ganglion cells, may have some bearing on this problem. In any case the intricate histology and the complicated synaptic events seem to justify the conclusion that the conventional diagrams of the synaptic connections in autonomic ganglia can no longer be assumed to give true pictures of the function and organization of the ganglia.

A new feature in the picture of the autonomic ganglia was introduced by the discovery by Marrazzi (306) that epinephrine has an inhibitory effect on ganglionic transmission. The effect can be produced by epinephrine liberated from the adrenal medulla and may thus be of physiological significance (305, 308, 346). Marrazzi has interpreted this as a "self-limiting mechanism in sympathetic homeostatic adjustment." It has been found that an epinephrine-like substance is liberated in ganglia on preganglionic stimulation (58) which, according to Marrazzi (307), suggests that epinephrine may be a humoral inhibitor at ganglionic synapses. The existence of inhibitory fibers in autonomic ganglia, once postulated by Eccles (118), and the importance of locally liberated epinephrine as inhibitor have been seriously questioned, however (232, 298). On the basis of recent quantitative studies of the secretion rate of epinephrine from the adrenal medulla on strong reflex excitation (cf. 81, 152), it seems questionable whether epinephrine from this source may play any important role as a regulator of ganglionic transmission.

PHYSIOLOGICAL DISCHARGE RATE IN PERIPHERAL AUTONOMIC NERVOUS SYSTEM

It has long been known that many autonomic effectors, even under 'resting' conditions, are usually more or less influenced by a tonic activity in the nerves supplying them and that this tonic control may be rapidly changed into strong excitation or inhibition of the effectors by reflex stimulation of the autonomic nervous centers. From several points of view it is of importance to know the discharge rate in the different states of activity. A brief survey of studies pertinent to this problem is therefore necessary.

One of the early significant facts observed was that the response of an autonomic effector on preganglionic stimulation is not maintained if the stimulation frequency is relatively high (>20 to 40 per sec.) (25, 247, 256, 333, 365). Even at a rate of 10 per sec., fatigue may set in rapidly (25). Recording of the postganglionic action potentials showed, furthermore, that at frequencies above approximately 20 per sec. an increasing asynchronism of the postganglionic discharge appears and that ganglion cells progressively drop out of action (44, 47, 69, 276, 277).

Another significant fact is that strong responses from various effectors are obtained at low frequency stimulation. Rosenblueth (361) found that a frequency of 15 to 25 per sec. produced approximately maximal responses in all the sympathetic effectors examined by him. The same or often even lower values have been found in other studies (37, 158, 246, 297, 332, 368, 369). Recent work on vasomotor fibers to various tissues has demonstrated that almost maximal vasoconstriction or vasodilatation can be obtained at discharge rates of about or below 10 per sec. (cf. 81, 152).

The studies referred to above suggest that the upper limit for the physiological discharge rate does not exceed about 20 per sec. However, there is evidence from observations of a more direct nature strongly indicating that this limit is reached at considerably lower frequencies and that tonic control is exerted at very low discharge rates. By recording from single or a few sympathetic fibers Bronk and his associates (43, 45, 46, 344, 345) were able to show that there is a continuous discharge of impulses with frequencies down to and below 1 per sec. during 'resting' conditions and that even intense reflex stimulation seldom increased the rate above 10 to 15 per sec. In similar experiments with parasympathetic fibers to the bladder Evans (140) observed a tonic discharge rate below 1 per sec. With well-controlled quantitative methods Folkow (150, 151) compared in cats the constrictor tone in an isolated vascular area on reflex excitation of the vasomotor center and on stimulation of the constrictor fibers. The experiments clearly demonstrated that the constrictor tone present at normal arterial pressure values could be maintained by 1 to 2 impulses per sec., that almost maximal vasoconstriction is obtained at frequencies of 6 to 8 per sec., and that the very high pressor reactions observed

on intense reflex activation of the vasomotor center could be obtained by an increase of constrictor fiber discharge from 2 per sec. to 5 to 6 per sec. Other experiments concerning the local elimination and exhaustion of the vasoconstrictor transmitter support Folkow's conclusion that the upper limit of the physiological discharge range is 6 to 8 impulses per sec. The validity of this conclusion has been confirmed by experiments using several other effectors of a very different nature (81, 82, 154). The study of Celander (81) in particular shows that most effector systems may give very pronounced responses at remarkably slow firing rates of the autonomic nerves (0.25 to 2 impulses per sec.). (See Chapter VII on autonomic neuroeffector mechanisms by von Euler in this work for further discussion of this topic.)

ACTIVITIES OF PERIPHERAL AUTONOMIC NERVOUS SYSTEM INDEPENDENT OF CENTRAL NERVOUS SYSTEM

'Spontaneous' Activity

Since the work of Bronk and his associates, it is well known that the autonomic nerves exert a tonic activity by a more or less continuous, usually characteristically grouped discharge, evoked particularly by various afferent reflex mechanisms. If this afferent driving is cut off, usually no activity is found in the pre- and postganglionic neurons. Some exceptions have been observed, however.

Alexander (4) recorded a persistent residual tonic activity in the inferior cardiac nerve of the cat when all afferent impulses to the preganglionic cells had been excluded. The activity showed a definite reduction when the arterial pressure was increased, thus imitating the behavior in animals with intact afferents. The experiments indicated, however, that the phenomenon was caused by lowered oxygen and increased carbon dioxide tension in the spinal cord. An observation more difficult to explain was made by Keller (238). In cats with deafferented oculomotor nuclei the pupils were constricted for several weeks, supposedly owing to persistent constrictor tone as the pupils dilated on local application of atropine. However, this assumption was not controlled by nerve section and no further analysis of the mechanisms was performed.

It has been claimed that denervated autonomic ganglia may have some autonomous activity (35, 140, 172–175, 198). There is no evidence that the phenomena observed have any physiological significance and they may well be explained on the basis of two facts. Autonomic ganglia develop supersensitivity at denervation (see the section on degeneration and regeneration in the peripheral autonomic nervous system) and there may be a slow continuous release of the chemical mediators from the postganglionic nerve terminals similar to that found in motor end plates (141, 143). In the studies of Govaerts (172–175) and Evans (140), for instance, the recorded postganglionic discharge from isolated ganglia may have been due to supersensitivity as the discharge did not develop or was not observed until several days after the denervation. The observations of Tower & Richter (415), assumed to give evidence of some independent activity in sympathetic ganglia, have been shown by Hare (190) to be due to incomplete denervation. Hare and others (3, 4, 50, 200) have not been able to find any such activity. The discharge occasionally seen when recording from postganglionic fibers in acute experiments is most probably produced by injury to the ganglia (3, 440).

Axon Reflexes

Some curious reflexes mediated through decentralized autonomic ganglia were shown by Langley (263, 269) to be caused by preganglionic collaterals to different ganglia. Such a branching system is, as Langley demonstrated, a common arrangement in the preganglionic neuron. Stimulation of the distal part of a preganglionic fiber thus generally activates ganglia at the proximal part of the fiber. The Sokownin crossed bladder reflex, contraction of the bladder on stimulation of the central end of one cut hypogastric nerve, could be explained on this basis as evoked by impulses traveling up in preganglionic fibers destined to more distally located ganglia and giving off collaterals to the contralateral inferior mesenteric ganglion. The correctness of this explanation has been proved in neurophysiological investigations demonstrating that preganglionic B fibers traversing the ipsilateral ganglion are concerned in the reflex (230, 231, 293). Other examples of such preganglionic axon reflexes have been recorded by Langley (263) and others (109, 231, 330). The only evidence that pseudoreflexes of this type play any role except under experimental conditions comes from Hilton's studies of vasomotor axon reflexes which may participate in causing the postcontraction hyperemia of skeletal muscle.

Evidence for the view that axon reflexes may also be evoked in the terminal ramifications of postgan-

glionic fibers has been reported, although it is not always of a conclusive nature. In deafferented and preganglionically denervated frog legs Speranskaja-Stepanowa (394) observed vasoconstriction and vasodilatation in vessels of the web on faradic stimulation of various skin areas in the vicinity of and even far away from the responding vessels. The vasomotor responses persisted three to four days after section of the sciatic nerve but disappeared thereafter. On this basis they were interpreted as being caused by axon reflexes in branching postganglionic fibers. No evidence for the existence of branches supplying skin areas so widely apart has appeared since then. In apparently well-controlled experiments on human skin, Wilkins *et al.* (441) obtained a local sweat response within areas some centimeters wide on faradic stimulation of certain points of the skin, and the response was proved to be mediated by sympathetic sudomotor fibers. The same gland could be activated from different points up to 2 cm apart and the areas activated from any particular point showed considerable overlapping. It is apparent that the sudomotor responses are evoked by axon reflexes in terminal ramifications of postganglionic fibers, each of which branches near its innervation territory and sends filaments in all directions within a small skin area, and that these axon systems overlap each other to a considerable extent. Similar studies have been made on pilomotor fibers (289, 429).

Postganglionic axon reflexes have recently become of new interest from a pharmacological point of view. This started with the discovery by Coon & Rothman (87–89, 372) that drugs with nicotine-like action injected intradermally elicit sudomotor, pilomotor and vasomotor activity in areas surrounding the site of injection. As these responses are abolished by local anesthetics and by degeneration of the peripheral nerves, they are presumably evoked by axon reflexes. On the basis of the stimulating and the paralyzing action of drugs on the axonal receptor points, it was suggested that these points possess several properties characteristic of autonomic ganglia. This has been further stressed by later investigators who have shown that the excitatory action of the drugs on the receptor points is inhibited by ganglion-blocking agents (20, 114, 228, 428). Although the suggested analogy may have no physiological significance, interesting new views on the properties and organization of the peripheral autonomic innervation apparatus may come out of these investigations.

Other Types of Reflexes Mediated by Autonomic Ganglia

Although there is no proof that autonomic ganglia isolated from the central nervous system are able to exert an independent tonic activity, it does not follow that decentralized ganglia are unable to perform some kind of reflex activity. The old claim of Dogiel (106) that sensory neurons may be present in autonomic ganglia once gave rise to speculations concerning this problem. Dogiel's interpretations are quite unconvincing, however, and all the neurohistological work since then has failed to demonstrate their existence. Considerable physiological evidence has accumulated indicating the nonexistence of neurons subserving intraganglionic reflexes and the inability of isolated ganglia to exert reflex activities. Thus it has been shown, for instance, that stimulation of one of the sympathetic postganglionic nerves to the heart does not give rise to discharge in another of these nerves, a fact indicating that no afferents connect with the postganglionic neurons in the stellate ganglion (49, 69). Another example is that no vasomotor reflexes mediated through the ganglia of the sympathetic trunk are observed after destruction of the spinal cord or after preganglionic denervation (4, 14, 34, 201). Two studies are often taken as evidence for an independent ganglionic reflex activity. In one of them (380), it was claimed that sudomotor activity could be evoked in the cat's forepaw by a reflex solely involving the stellate ganglion. This has been shown to be due to an incomplete decentralization of the ganglion (190). In the other study (440), a small discharge was found on stimulating one ciliary nerve and recording from another. As accessory ganglia are often present (442), this finding probably has its explanation in a preganglionic axon reflex.

There are many observations, however, indicating that the prevertebral ganglia have mechanisms mediating reflexes between different parts of the abdominal viscera. It has been claimed (157, 283, 284) that the decentralized inferior mesenteric ganglion exerts a motor control of the large intestine, but this does not necessarily mean the involvement of reflexes. In a series of investigations Kuntz and his associates (248, 249, 255, 254) have found that some synaptic structures persist in the celiac and the inferior mesenteric ganglia after degeneration of the preganglionic fibers and observed that intestinointestinal reflexes synaptically relayed in the ganglia could still be evoked after decentralization. These findings have been confirmed by Warkentin *et al.* (431), but severely

criticized by Freund & Sheehan (156) on the basis of the extreme difficulty of obtaining a complete decentralization of the abdominal ganglia. In animals sympathectomized according to Cannon, they were not able to obtain any intestinointestinal reflexes. However, the experiments of Freund & Sheehan do not give any explanation for the significant observation of Kuntz that intact nerve fibers remain in the distal stump of the cut colonic or mesenteric nerves after degeneration of the fibers coming from the ganglia. If regeneration can be excluded, as claimed, the undegenerated fibers must arise from neurons in the intestinal wall and may thus be the afferent link in the reflexes observed.

The view of Kuntz that there are afferent neurons in the intestinal wall synaptically connected to efferents in the prevertebral ganglia has support from recent neurophysiological studies. On stimulation of the central stump of the cut hypogastric nerve in the cat Job & Lundberg (230, 231) recorded reflexes involving C fibers in both the contralateral and the ipsilateral colonic and hypogastric nerves. By degeneration experiments it was shown that the fibers giving rise to the C reflexes must have their trophic centers distalwards and that they terminate in the inferior mesenteric ganglia. Brown & Pascoe (54) and McLennan & Pascoe (310) have made similar observations in the rabbit. In the mesenteric nerves leaving the inferior mesenteric ganglion they showed the presence of a distinct group of nerve fibers with cell bodies possibly located in the gut and terminating in the ganglion. The fibers belonging to this group have a remarkably low conduction velocity (0.25 m per sec.) and are connected to cells with axons of the common C type returning along the same nerves.

The studies of the inferior mesenteric ganglia seem to make it necessary to postulate the existence of reflex systems involving synaptically connected neurons wholly confined to the peripheral autonomic nervous system.

The enteric plexuses have long been regarded as holding a unique position in the autonomic nervous system. It may be assumed that local reflexes can take place here, but the nature of and the anatomical substratum for such reflexes are unknown. On the basis of the old experiments made by Magnus on ganglion-free intestinal walls it has often been concluded that the spontaneous contractions of isolated intestinal segments are of nervous origin. However, all the subsequent work in this field has clearly shown this conclusion to be invalid. In the recent careful study of Evans & Schild (138), it was demonstrated that plexus-free circular muscle of cat jejunum exhibits rhythmic activity in response to raising of the intraluminal pressure. It is very difficult to decide to what extent the movements of the intestinal wall are dependent on intraganglionic reflexes. Much work has been done using nicotine to paralyze the intramural ganglia but the results are controversial, and it is now well established that this drug has effects on many structures other than ganglia (cf. 131, 138, 144, 419). From studies of the action of the ganglion-blocking agent hexamethonium Feldberg (144) concluded that some spike-like contractions and contractions of composite character are ganglionic in origin. On the other hand, hexamethonium did not affect the large, rhythmic contractions of the longitudinal muscle in rabbit ileum preparations. However, this drug may have effects on smooth muscle also (139).

EFFECTS OF DECENTRALIZATION OR DENERVATION ON AUTONOMIC EFFECTORS

Effects on Structure and Activity of Effectors

No gross anatomical changes are seen after sympathectomy even if denervation is performed early in life (71, 309, 412) and the tissues show, with some exceptions, a normal histological appearance (85). Denervated smooth muscles do not atrophy or degenerate, and no obvious cytological changes have been found in the cells. Sweat glands have been reported to atrophy (414) or to be unaffected (85, 184, 229) after sympathectomy. Cytological changes, inconsiderable to very marked, and even a substantial atrophy may develop in salivary glands with severed secretory nerves (11, 128). The denervated adrenal medulla, on the other hand, has quite normal cytology (199, 208).

It is not as yet possible to explain why some effector cells atrophy after section of their autonomic nerves. It seems reasonable, however, that the structural changes found in some glands are wholly due to lack of adequate secretory stimuli. This view is supported by the findings that it is possible to obtain the same histological changes in the cat's submaxillary glands both by atropine treatment and by severing the chorda tympani, and that pilocarpine reverses the changes in decentralized glands (132).

Neither decentralization nor denervation seem to alter to any appreciable extent the basic properties of smooth muscle or gland cells, as chemical stimuli may evoke the same maximal contractile or secretory re-

sponses as before severance of the nerves. Considerable differences in the state of activity are found in different effectors deprived of their autonomic nerves, however. The cells of the adrenal medulla and of the salivary and sweat glands show little if any activity. This also holds for some smooth muscle, such as the pilomotor, the orbital and the intraocular muscles. The activity of most smooth muscle, on the other hand, is more or less uninfluenced by denervation and exhibits various types of rhythmic contractions, spontaneous in the sense that they are independent of nervous impulses mediated through autonomic ganglia. Several investigators have believed this spontaneous activity (e.g., 6, 148) to be dependent on a terminal nervous network which does not degenerate after postganglionic nerve section. As will be shown in a later section, there is no valid evidence for the existence of such a structure but much good evidence pointing in the other direction. Studies of the propagated contractions and of the origin and conduction of action potentials in smooth muscle from the uterus, ureter, intestine and stomach, especially by Bozler (38–41, 217), have laid a good foundation for the view that the spontaneous rhythmic contractions are of myogenic origin and that conduction proceeds from muscle cell to muscle cell and not through a nervous network. This view has received strong support from recent work by Bülbring (59, 60), Evans & Schild (138), and by Prosser and his associates (347). Whether conduction takes place in a syncytium of muscle cells (Bozler, Bülbring) or perhaps by a sort of ephaptic system between muscle fibers (Prosser) has not yet been settled. Electronmicroscopic studies of smooth muscle from rat ureter have, however, demonstrated a lack of protoplasmic continuity between the cells and have revealed intercellular bridges assumed to be ephaptic structures (19).

That the smooth muscle of small blood vessels regains its tone to a varying degree after denervation is well-known and has usually been explained on the basis of supersensitivity (cf. 15). Strong arguments against this theory have been presented by Cannon (73) in experiments indicating that the recovered tone might be due to intrinsic properties of the muscle cells. There is now good evidence for the view that the smooth muscle of blood vessels has a myogenic automaticity like that found in, for instance, ureteral muscle (cf. 82, 152).

Supersensitivity of Autonomic Effector Cells

It has long been known that various types of autonomic effector cells deprived of their pre- or postganglionic nerve supply undergo changes leading to a state of increased sensitivity to epinephrine, norepinephrine, acetylcholine and other agents. As the investigations into this phenomenon have recently been extensively reviewed by Cannon & Rosenblueth (77), only a brief survey will be given.

The supersensitivity of various smooth muscles shows some common features such as increased susceptibility and increased duration of response to a given agent, but the maximal response does not become larger than in the muscles prior to denervation. This also holds for glands (128, 399). The increased sensitivity may develop quite rapidly, in some instances within hours, as reported for the denervated pupillary sphincter in the cat (388), or may become maximal within two to four days as reported for the sweat glands (391) and for the pupilloconstrictor (237). In adrenergic systems the development of supersensitivity generally takes a more prolonged course, maximal sensitization being found after 2 to 3 weeks. The new state of excitability seems to remain permanently, at least in most instances, but disappears when regenerating nerve fibers become functionally connected to the effector cells (389).

Supersensitivity has been shown to develop in the most different cholinergic and adrenergic systems supplied by both excitatory and inhibitory fibers. Decentralized nerve cells in autonomic ganglia are no exception (129, 364, 390). As might be expected, a decentralized effector is supersensitive not only to agents introduced from outside but also to the transmitter liberated by stimulation of the postganglionic nerve fibers (363). Finally, another general principle is that denervated systems develop a higher degree of supersensitivity than decentralized ones.

The general principles for the development of supersensitivity were formulated in 1939 by Cannon into a 'law of denervation': when in a series of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effects being maximal in the part directly denervated. This has been confirmed on the whole by the subsequent work in this field. Some exceptions have been reported, however. Denervated sweat glands in man, for instance, have been claimed to be desensitized (229) or to be unresponsive after some time (216). The sensitivity of sweat glands in the cat has been found to decrease a long time after denervation (391). Conflicting results have been obtained as regards the denervated heart (176, 220, 295). The evidence does not seem to be conclusive.

There is as yet no generally accepted explanation

as to why nerve section is followed by supersensitivity. Although it is not impossible that the nerve terminals might liberate, in addition to the chemical mediator, some other substance of importance for the effector cells, the concept of a trophic influence exerted by the nerves is difficult to accept. The most reasonable explanation seems to be that supersensitivity develops owing to lack of transmitter stimuli. The arguments and evidence against this view brought forth by Cannon & Rosenblueth (77) do not seem to have validity any longer. On the contrary, this explanation has received strong support from the extensive studies of the supersensitivity of salivary glands made by Emmelin and his associates (cf. 128). The most pertinent results are that a supersensitivity, indistinguishable from that found after nerve section, may be evoked in nondenervated glands by preventing the chemical mediator from acting on the cells, and that supersensitivity due to nerve section may be prevented or abolished by exposing the cells to chemical stimuli of a secretory nature. The concept of a trophic influence hardly seems compatible with these results. The fact that supersensitivity is less pronounced after decentralization than after denervation may, according to this view, be explained as due to intermittent release of small quantities of the transmitters from the postganglionic nerve terminals (see the previous section on activity independent of the central nervous system).

In spite of much work, no theory has been elaborated which is able to give a satisfactory explanation of the changes resulting in supersensitivity. Cannon & Rosenblueth (75) once suggested an increased permeability of the cells to be the basic change. Although at least suggestive evidence for this theory is available, the experimental data are difficult to explain on this basis. Burn and his associates have tried in a series of investigations (62–66) to furnish evidence for the hypothesis that supersensitivity is a consequence of a decreased ability of the effector cells to inactivate the chemical mediators. For some smooth muscles it was found that the increase in sensitivity after denervation paralleled a fall in amine oxidase and in cholinesterase, which clearly supported their theory, but in other muscles no such correlation could be demonstrated. This lack of correlation has also been found by other investigators (10, 401). Another difficult obstacle for the theory is that denervated effectors develop hypersensitivity to many substances quite unrelated to the natural transmitters. Some of the nonspecific agents were shown to act indirectly by liberation of an epinephrine-like substance, but the effects of other drugs may be more difficult to explain (cf. 221, 222, 400).

DEGENERATION AND REGENERATION IN PERIPHERAL AUTONOMIC NERVOUS SYSTEM

Degeneration

The structural changes initiated in autonomic nerve fibers by transection are very similar to those of somatic fibers, at least when examined with neurohistological methods. The myelin sheath, when present as a microscopic structure, is retracted from the nodes and broken up in fragments, the axon is fragmented and disintegrated, and finally both undergo dissolution. There are many controversial statements as to the degeneration of the autonomic nonmedullated fibers and no systematic research has been done on this matter. It is often stated that these fibers are considerably more resistant than the myelinated. This view was generally accepted in classical neurohistology (28, 337, 349, 410). Ramón y Cajal (349), for instance, stated that sympathetic nonmedullated fibers do not disintegrate until 4 to 7 days after transection. In many later studies it has been found, however, that both pre- and postganglionic nonmedullated axons in the cervical sympathetic of the rat, rabbit and cat show degenerative changes as rapidly as large somatic nerve fibers and disintegrate within 24 to 72 hours. This has been demonstrated both by the silver impregnation technique (97, 103, 279, 282, 301) and by methylene blue staining (170, 206, 416). The nonmedullated fibers in fine skin nerves also degenerate rapidly (434). It may well be, however, that there are large differences between different autonomic nerves. Some support for this view is given by the varying reports on the functional degeneration of sympathetic C fibers. There is evidence, for instance, indicating that the sudomotor fibers in the cat's paw may conduct impulses up to 6 days after nerve section (391). Such a long degeneration time, however, may also be found in some instances for preganglionic B fibers in the cat's cervical sympathetic (see e.g. 168, 286). The responses obtained on stimulation of degenerating autonomic B (see below) and C (301, 416) fibers usually decline rapidly to disappear within 2 to 4 days, but this is no evidence for a loss of conduction. On the basis of the available sparse and unsystematic reports, it is not possible to decide whether the autonomic B and C fibers differ markedly from each other or from somatic

fibers. There is no conclusive evidence for the view adopted, for instance by Rosenblueth (292, 366, 367), that the autonomic C axons in general degenerate considerably more slowly than large somatic fibers, which usually show conduction failure 2 to 4 days after transection (80, 135, 292, 366). The slowest known autonomic C fibers lose the ability to conduct impulses within 5 days, as shown by direct recording (310).

In the course of the Wallerian degeneration of preganglionic fibers, synaptic transmission fails at a stage when impulse conduction may be largely unimpaired (90). Usually transmission declines rapidly between 24 and 48 hours after nerve section, to disappear within 72 hours (13, 97, 90, 206). This is in good agreement with the time range reported for the transmission failure in voluntary muscle (292, 367, 407). Rosenblueth has concluded (cf. 362) that synaptic failure is not due to an early degeneration of the nerve endings, as suggested by Titeca (411), but to a decrease of the acetylcholine liberated by the nerve impulses. There is good evidence that acetylcholine is concentrated in the nerve endings and that it disappears, and the endings lose to a high degree the ability to synthesize acetylcholine after preganglionic transection at the same time as the transmission fails (13, 142, 302, 303). Furthermore, as both the structural and functional degeneration seem to have a progressive centrifugal course (80, 292, 366), the conclusion seems to be justified. It may be questioned, however, whether the demonstration of progressive degeneration in the nerve trunk is conclusive evidence against the occurrence of an early degeneration of the nerve endings. Axon terminals in the motor end plate, for instance, seem to disintegrate earlier than the supplying fibers (206). This may be the case also for the terminal intraganglionic fibers (103).

Slight changes in the Nissl substance and some cell shrinkage have been reported to occur with preganglionic degeneration (189, 282, 328, 397), but this has been questioned (374). Apart from supersensitivity, chronically denervated ganglia show altered reactions to ganglion-blocking agents, suggested to be due to a fall in the intracellular potassium content (338, 339).

The retrograde reaction in autonomic ganglia initiated by section of the postganglionic nerves produces cytological changes similar to those seen in somatic neurons and recently the similarity has been found to extend to the functional changes (1, 2, 55). After axotomy of the postganglionic neurons, impulse transmission in the ganglia is rapidly impaired and almost completely abolished within 2 weeks. Later there is a slow recovery stage. Many of the cells have become irreversibly changed, however, as both the transmitted response and the spike potential obtained by direct stimulation of the postganglionic nerve are markedly reduced. The transmission failure seems to be due to changes in the soma of the postganglionic cells resulting in a loss of sensitivity to liberated transmitter.

Regeneration

The data hitherto reported concerning the various aspects of regeneration in the autonomic nervous system are incomplete, unsystematic and often highly contradictory. It is not therefore possible to treat this subject more than purely superficially. Regeneration in the peripheral nervous system has recently been reviewed (185).

Whether regeneration of autonomic nerve fibers differs fundamentally from that of somatic fibers has not been adequately studied. That such differences may exist in the case of nonmedullated fibers is suggested by the report of Nageotte (325) that their sheaths form a syncytial network. Nonmedullated fibers often are composed of a sheath enclosing several fibers (162, 204, 325). Again, the Schwann cells of autonomic nonmedullated fibers do not multiply after nerve section (235, 236, 416). Nevertheless, such studies as have been made of regeneration of autonomic fibers have failed to reveal obvious differences from that of somatic fibers (97, 98, 279, 282).

From data obtained by indirect methods (56, 57, 285, 286, 334, 413) the rate of growth in the cervical sympathetic trunk of the cat, rabbit and dog may be estimated to be 1 to 2 mm per day if scar and maturation delay are taken into account. This is in good agreement with values found in a more systematic study of cat and rabbit (67) where the rate of advance of functional recovery after crushing the cervical sympathetic trunk was estimated to be 2 mm per day for the cat and to 1.6 mm per day for the rabbit. The functional return, as determined by the disappearance of paralysis after section or crushing of the cervical sympathetic trunk in the cat, has been reported to occur within 2 to 6 weeks depending on the site of lesion (56, 57, 67, 286, 389). In some animal species (especially the cat) the preganglionic fibers have a high capacity for bridging even very large gaps (67, 206, 239–241, 286); in other species (the rabbit for instance) this capacity is, on the contrary, very restricted (67). It is possible that the differences are

ultimately dependent on whether the fibers are myelinated or not. Data concerning the regeneration of the nonmedullated fibers in the cervical sympathetic trunk of the rat (206) speak against this view, however.

The regeneration of the nonmedullated preganglionic fibers in the rabbit vagus has been found to be largely dependent on the site of the lesion (137). If the abdominal vagi are crushed, a delayed functional recovery of the stomach is obtained but, if the nerves are crushed in the cervical region, function does not return within 600 days. This was found to be due to a growth of the parasympathetic fibers into the recurrent laryngeal nerve, the fibers apparently being 'guided' along the medullated fibers. The syncytial character of the sheaths of the nonmedullated fibers was suggested to be the causal factor for this diverted regeneration. Regeneration of vagal fibers to the heart after high lesions of the vagus nerve in cat and rabbit may take place, however (68).

Only very incomplete data are available concerning the regeneration of postganglionic fibers. Apparently, a functional recovery is obtained with great difficulty, if at all, when the fibers to the cat's forelimbs are cut in the grey rami (239, 414). The postganglionic fibers from the superior cervical ganglia regenerate and give at least partial return of function after a long period in the rabbit (416) but relatively rapidly in the cat (301, 389). It is obvious that the regenerative capacity may to a large degree be invalidated by a severe axonal reaction if the lesions are situated near the cell bodies of the cut fibers, which may lead to cell death (282, 288).

When functional regeneration has set in, a stage of overcompensation may develop manifested by such signs as a large pupil, exophthalmos and constricted vessels (56, 57, 286, 301). This phenomenon is probably a consequence of the denervation supersensitivity (389).

That denervated tissues may be reinnervated by outgrowth from intact nerve fibers in the vicinity is well-known in the somatic system (cf. 125). Evidence has been given for collateral regeneration of sudomotor fibers in the cat's paw (212) and of preganglionic fibers in the cat's partially denervated stellate and superior cervical ganglion (165, 324).

Practically nothing is known about the maturation process of regenerating autonomic nerve fibers. Functional recovery in the cat's superior cervical ganglion may take place at a stage when the regenerating fibers have still not been myelinated (67) and may show an impulse conduction velocity as slow as C fibers (168).

Heterogeneous Regeneration

In a series of well-known experiments, Langley & Anderson (9, 262, 264, 271, 272) showed that the peripheral nerve fibers could be divided into three groups with regard to their ability to replace each other: efferents from the spinal cord, postganglionic fibers and afferents. After cross-union, any particular nerve within each of the first two groups is able to establish functional connection with the peripheral part of another nerve belonging to the same group. They found, however, one puzzling exception: the ciliary preganglionic fibers were able to replace the postganglionic in innervating the pupillary sphincter. This existence of separate classes of nerves was logically explained when Dale (92) pointed out that the nerves in the first group are cholinergic and in the second adrenergic. As the postganglionic fibers to the pupillary sphincter were found to be cholinergic, this exception in the system of Langley and Anderson only confirmed the view that the compatibility of nerves when cross-united is determined by the chemical mediator.

The observations of Langley and Anderson have been amply verified. Heterogeneous regeneration has been demonstrated to give functional connection between various somatic motor nerves and the superior cervical ganglion (16, 99, 100, 111, 443), between parasympathetic preganglionic fibers in the vagus and this ganglion (16, 97, 99, 100, 186, 206), and between preganglionic sympathetic fibers and somatic motor nerves (18, 206). Afferent fibers have been claimed to provide functional innervation of voluntary muscle (436), but careful experiments have shown this not to be the case (187, 437). There is evidence that parasympathetic fibers to the salivary glands may be misdirected by nerve lesions and give functional innervation of sweat glands (395). Thus, there is considerable evidence supporting the view of Dale. The ability of neurons to liberate a certain chemical mediator by nerve impulses in themselves nonspecific is thus a property inherent in specific types of neurons.

There are some results as yet unexplained, however. The sensory root fibers of the nodose ganglion have been stated (101, 102) to achieve synaptic connections with the postganglionic neurons in the cat's superior cervical ganglion. Another peculiarity, as shown by Anderson (9), is that no functional connection is established between the preganglionic oculomotor nerves and the pupillary sphincter since stimulation of the nerves did not elicit any response.

This inability to produce exciting junctions in spite of very favorable conditions for regeneration (myelinated postganglionic fibers and a ratio of preganglionic fibers to postganglionic neurons of about 1:2) needs explanation (cf. 206, 300).

STRUCTURE AND FUNCTIONAL ORGANIZATION OF AUTONOMIC EFFECTOR JUNCTIONS

The neurohistological investigations of the last twenty years have given rise to many highly divergent opinions on the structure of the autonomic innervation apparatus. The nonspecificity of silver impregnations is well-known and it has been clearly shown that the fixation procedure and other treatments of the tissues when using these methods give rise to misleading artefacts (203, 206, 210, 243, 280, 435). In spite of this, many prominent neurohistologists, for instance Stöhr, Boeke and their students (see e.g. 30, 403), claim that the peripheral extensions of the autonomic nerve fibers have a syncytial construction and a continuous neurofibrillar connection with a network located within the innervated cells, a network with fibrils of such fine dimensions that they are near the limit for the resolving power of the microscope. It is obvious that the claims made by Stöhr and Boeke cannot be accepted until very strong evidence has been furnished that the structures demonstrated are both of nervous nature and existent in the living tissues. No such evidence has yet been presented, however, neither in their earlier (cf. 206) nor in their more recent papers (33, 355, 404-406). Furthermore, their results concerning the microscopic appearance of the nervous syncytia are quite different and partly incompatible in spite of the fact that both Stöhr and Boeke use silver impregnations and that they both argue along the same lines for the validity of their views. This gives a good illustration of the difficulties inherent in their methods. A detailed criticism of their neurohistological studies has been published (206). In the discussion of the 'interstitial cells' (see below), another example will be given illustrating the general tendency to draw far-reaching conclusions concerning the presence of histological structures, the nature and function of which have been interpreted without rigid criteria for their characterization.

Up to 1932 the autonomic effector cells were considered to be innervated by postganglionic fibers terminating in extra- or intracellular nerve endings. Recently the existence of far more extensive nerve structures has been claimed. Stöhr described a 'terminal reticulum' composed of sympathetic and parasympathetic endings which anastomose with a syncytially constructed network partly embedded in the cytoplasm of the innervated cells. Boeke proposed a 'sympathetic ground plexus', arising from coarser nerve fibers which connect with a fine-meshed protoplasmic network containing extensively anastomosing neurofibrils. This network is distally in protoplasmic continuity with a system of 'interstitial cells', interpreted as nerve cells, which in turn make synapse-like connections with the effector cells (33). Boeke's descriptions of the proposed structures are unconventional and confusing (27, 29).

The postulation that the interstitial cells of Ramón y Cajal constitute third neuron links in peripheral autonomic innervation (30-32, 224-227, 287, 312, 314, 315, 326, 327) deserves critical comment as this concept may become of importance in physiology (cf. 6, 152). The evidence claimed for the view that the interstitial cells are in fact nerve cells and not sheath cells is as follows (32, 33, 224-226, 287, 312-314): *a*) their cytological characteristics are the same since they are vitally stained by methylene blue, contain Nissl granules and neurofibrils, and show positive oxidase and peroxidase reactions; and *b*) they do not degenerate following postganglionic section. However, much of this is disputed, both as to the findings and as to their interpretation (21, 206, 290, 331, 396).

In view of the inconclusiveness of the neurohistological evidence, the concept of a terminal syncytium of nerve cells interposed between the postganglionic nerve endings and the effector cells cannot be accepted. There is no reason to suppose that the cells are anything but neurilemma cells, as suggested long ago by Lawrentjew, Stöhr, de Castro, Schabadasch, Nageotte and others, and strongly supported by the recent careful studies of Greving (181, 182) and Herzog (203).

However, certain physiological and pharmacological findings have been believed (6, 148, 417, 418) to indicate the existence of a terminal nervous syncytium, e.g. the diffuse character of the responses obtained on stimulation of a small proportion of the nerves supplying the smooth muscle of an organ. Strictly localized responses are often found in smooth muscle (8, 110, 127, 169, 211, 266, 300, 321), and the diffuse responses usually obtained were adequately explained by Langley (266) as being due to "the intermingling of the postganglionic fibers which occurs in the preterminal plexus on the way to the

tissue." Further, since conduction through smooth muscle is not inhibited by local anesthetics (38, 60, 146, 393) or by ganglionic blocking agents (60, 126, 144, 379), it is doubtless myogenic and therefore does not require conduction through a peripheral nerve net (148, 377).

Two further considerations oppose the acceptance of such a nerve net. First, the innervation of smooth muscle in certain organs, such as the heart (370), the cat retractor penis (332), certain small blood vessels (300), the cat submaxillary gland (130, 299) and fish melanophores (335), by two sets of fibers with antagonistic actions seems incompatible with a syncytially connected peripheral net (377). Second, the assumption that the terminal parts of the autonomic innervation structure may remain more or less intact after degenerative transection of the postganglionic nerves, a correlate to the syncytium theory, does not fit the evidence presented by von Euler and his associates (171, 424, 425, 427), strongly indicating that the adrenergic transmitter is accumulated in the nerve terminals and clearly showing that it disappears when the postganglionic fibers degenerate.

The neurohistological investigation referred to above led to a new concept of the innervation of autonomic effectors according to which the innervation takes place by means of the autonomic ground plexus, a plexus of axon ramifications embedded in a fine-meshed network of anastomosing protoplasmic strands formed by the terminal Schwann plasmodium and directly superimposed on and probably contacting all effector cells. The view that the plexus is the real innervation structure is partly hypothetical as it is based on the assumption that the plexus is a closed terminal formation. The structure of the plexus regarded as a whole strongly supports this concept.

The morphological arrangement of the autonomic ground plexus does not in itself give any clue to the functional organization of effector innervation. Cannon, Rosenblueth and their associates (cf. 76, 361, 368, 369) made the basic experiments necessary for an understanding of this organization more than 20 years ago, and they developed a theory giving a logical explanation to the phenomena observed. This theory is founded on the assumption that only some of the effector cells are directly innervated. The chemical mediator liberated by the nerve impulses in or at these 'key cells' diffuses to the non-innervated cells; this free diffusion explains their fundamental observation that spatial and temporal summation are quantitatively interchangeable in autonomic effectors, the response being dependent on the number of impulses per unit time only and not on the number of activated nerve fibers. In contrast to voluntary muscle, autonomic neuroeffectors are thus not organized in units, but the innervation is quite diffuse. Now it is obvious that the key cell principle is no necessary part of the theory and may be dropped, as apparently it has been by Rosenblueth (362). The essential parts are the theoretic aspects of the liberation, diffusion and action of the mediator. Much evidence in favor of the Cannon-Rosenblueth theory has accumulated (cf. 362), and certainly any new theory concerning the innervation of autonomic effectors must be able to account for the phenomena of spatial and temporal summation in the effectors.

Although leakage of the adrenergic mediator into the blood and diffusion within autonomic effectors have been demonstrated to occur, it may be that this diffusion does not have any physiological significance for the innervation of an effector system. Direct evidence concerning this problem has been obtained from studies of the cytologically demonstrable cell reactions evoked by reflex stimulation of the nervous centers of the adrenal medulla (206) and of the submaxillary gland (207) with intact innervation or partial denervation. Lack of space does not permit more than a brief summary, but a detailed discussion of the validity of the conclusions is found in the original papers. (See also Chapter VII by von Euler on autonomic transmission in this work.)

Both in the cholinergic systems and in the adrenergic system examined in the experiments, the results speak for the view that the cell complexes are organized in units which may be submaximally stimulated or drop out of activity altogether when the glands are partially denervated. The presence of more or less submaximally activated complexes in spite of intense stimulation, producing exhaustion changes in cells with intact innervation, indicates that each unit receives nerve terminals from several neurons. The results further speak strongly against the assumption that transmitter diffusion is an important innervation mechanism. For instance, denervated cell complexes do not show any activation through mediator diffusion from highly active complexes immediately adjacent to the denervated ones in spite of very intense stimulation of long duration, denervation supersensitivity and cholinesterase inactivation. These results are obviously inconsistent with the transmitter diffusion theory of Cannon and Rosenblueth. However, it is possible to form a new concept of autonomic

innervation which may give an alternative explanation for the observations of temporal and spatial summation in autonomic effector systems and furthermore an explanation for some of Rosenblueth's observations not accounted for in his theory. This concept, which also gives a reasonable explanation of the puzzling morphological construction of the innervation structure, especially the existence of several axons in each strand of the plexus, may be briefly summarized as follows.

The innervation structure consists of the autonomic ground plexus within which each terminal axon ramification has a certain extension and in its course innervates a certain number of cells or cell complexes forming a neuroeffector unit. To each unit, however, several postganglionic neurons converge, the terminal axon ramifications of which run within the same strands of the ground plexus. By the overlap thus present in the innervation structure the response of the effector system may be modified by both temporal and spatial summation.

It is obvious that this concept in no way contradicts the arguments and concepts of Cannon and Rosenblueth concerning the liberation and action of the chemical mediator. The mediator diffusion principle is replaced by a convergence principle on the basis of which several experimental results inconsistent with the diffusion theory may be logically explained. As the discrepancies have not been pointed out by Rosenblueth, some of them will be briefly discussed. From the crucial experiments on temporal and spatial summation in the nictitating membrane made by Rosenblueth & Rioch (369) it is clearly seen that, according to the diffusion theory, the mediator, locally liberated on stimulation of large or small fractions of the nerves, must be assumed to have a free diffusion to remote cells which is as complete and of the same effective magnitude when large or very small quantities are diffusing and when the diffusion distance is long or short. This seems quite unreasonable. The convergence principle, on the other hand, gives an adequate explanation to the experimental data; the spatial relationship between the site of release and the site of action of the mediator does not change when only a fraction of the nerves instead of all are stimulated. It can be seen from the same experiments that the mediator locally liberated by impulses in only a fraction of the nerves to the nictitating membrane must, according to the diffusion theory, be assumed to diffuse freely to all the muscle cells, even at the lowest stimulation frequencies (less than 1 per sec.). The results obtained in exactly the same type of experiments with chronic partial denervation of the membrane (246) are quite inconsistent with this view and do not indicate a mediator diffusion until a relatively high stimulation frequency is used. Finally, Rosenblueth & Rioch (369) have shown that cholinergic systems behave in the same manner as adrenergic systems with regard to temporal and spatial summation. This may be said almost to invalidate the whole diffusion theory. If it seemed unreasonable to have the same free diffusion of the adrenergic transmitter under all the experimental conditions examined, it certainly seems highly improbable to have such a diffusion mechanism in cholinergic effectors with their high power of destroying acetylcholine. The view that there exists a considerable convergence of nerve terminals from different postganglionic neurons to one effector cell group has strong support from a recent study of the electrophysiology of the cat's submaxillary gland (299).

It might be argued that the mediator overflow found to occur on stimulation of adrenergic nerves speaks in favor of the view that there is a considerable transmitter diffusion within autonomic effectors, a diffusion which has even been considered to make the concept of innervation quite illusory. Admittedly there is as yet no possibility of generalizing the innervation theory launched above to hold for all effector systems. However, the existence of the same innervation structure in widely different effectors and the possibility of giving a more adequate explanation of the summation mechanism in cholinergic as well as in adrenergic systems suggest a more general applicability of the theory. Furthermore, evidence is accumulating for the view that the adrenergic transmitters are to a large extent inactivated locally at the site of their release and that no significant accumulation or overflow take place on stimulation of adrenergic nerves with frequencies within the physiological range (81–83, 151). Quantitative determination of the norepinephrine output from the spleen on stimulation at different frequencies strongly supports this view (53).

There is good evidence that the chemical mediators are produced by and accumulated in the autonomic nerve terminals (cf. 362, 423–425). All the available data also speak for the view of von Euler that the mediators are concentrated in high amounts in the terminals. In fact, the amounts are so high that it seems necessary to postulate that the individual endings, each constituting a transmitting junctional structure, cannot be tiny knobs or small axon ex-

pansions but must have a considerable length. This is in good agreement with the assumption that the axon ramifications running in the autonomic ground plexus are real terminals releasing the transmitters when nervous impulses travel along them and thus acting on the effector cells with very short diffusion distances. This hypothesis makes it possible to explain the dual innervation of an effector cell without postulating the existence of two independent innervation structures for which there is no morphological evidence. It does not seem unreasonable that axon terminals from both sympathetic and parasympathetic neurons may be enclosed in the same ground plexus. On the contrary, all observations of the morphological construction of the plexus point in this direction. In this way both adrenergic and cholinergic mediators may be released from an innervation structure common to both autonomic systems.

FUNCTIONAL SIGNIFICANCE OF AUTONOMIC NERVOUS SYSTEM AND ITS SUBDIVISIONS

Our present knowledge of the basic coordinating functions of the autonomic nervous system is founded on the classical work of Cannon whose fascinating ideas and brilliant capacity for systematization have been of the utmost importance to the understanding of this system. Any attempts to give a brief summary of his contributions are doomed to failure but, fortunately, his work and views have been summed up in four monographs well-known today (70, 72, 76, 77). According to Cannon, the sympathetic and parasympathetic divisions are organized quite differently. The parasympathetic has a restricted distribution with more or less local functions, the cranial division as a 'conserver of bodily resources' and the sacral as a 'mechanism for emptying.' In contrast to this, the sympathetic has a widespread activity with a diffuse distribution of nerve impulses which makes it possible to call many different effectors into simultaneous play whereby a variety of functions serve to maintain homeostasis. Furthermore, the system subserves its general functions in intimate cooperation with the adrenal medulla, the hormone secretion of which supports the sympathetic activities. This cooperation is seen in many conditions of stress, above all in states of emergency, and is of such importance that the sympathetic division and the adrenal medulla may be considered as a sympathicoadrenal system.

In general, in organs innervated both by the sympathetic and parasympathetic, activation of these systems produces responses opposite in direction.

The validity of the concept of the sympathetic as a system maintaining homeostasis was elegantly demonstrated in experiments on sympathectomized animals (74, 376) which were shown not to differ markedly from normal animals under protected conditions but to have lost the ability to make acute adjustments when subjected to stress. The problems of autonomic regulations with regard to homeostasis have been extensively reviewed by Gellhorn (163). The concept of the sympathicoadrenal system as a cooperating unit has in a way received strong support from the more recent investigations into the role of the adrenal cortex in conditions of stress (cf. 422).

It is evident, however, that a sharp distinction between the sympathetic and parasympathetic cannot be made from a functional point of view. In certain effectors, such as the salivary glands, the two divisions show synergistic effects and this may be said to hold to some extent for the sphincter mechanisms in the gastrointestinal and urinary system also. Other effectors, such as the heart, have their activities delicately balanced by cooperation of the sympathetic and parasympathetic in a strictly reciprocal manner. The widespread diffusion of sympathetic impulses may in a sense be considered to be due not to an organization of the sympathetic system different from that of the parasympathetic but to the fact that the effector systems with the same general functions, e.g. the skin vessels, have a widespread distribution, and the diffuse character of some parts of the sympathetic may be considered to have its equivalent in the vagus system. There is, furthermore, good evidence that some parts of the parasympathetic division are activated and cooperate with the sympathicoadrenal system in conditions of stress (cf. 163). This has been shown to hold above all for the vagoinsulin system, the activation of which gives an insulin secretion interpreted to be an important adjustment enabling the striated muscles to utilize more fully the blood sugar which is increased by the activity of the sympathicoadrenal system (cf. 164).

The concept of the sympathicoadrenal system has unfortunately not been adjusted to the demands of the new evidence concerning the differences in actions and functions of epinephrine as a hormone with mainly metabolic effects and of norepinephrine as an adrenergic transmitter. Indiscriminate use of the concept has been criticized on this basis by von Euler (cf. 423–425). This subject is, however, dealt

with by von Euler in Chapter VII in this work dealing with autonomic transmission. The role of the medullary hormone secretion in the control of the various sympathetic effectors has recently been determined by quantitative methods (81, 154, 291). The results clearly show that the effectors are quite dominantly controlled by sympathetic nerve impulses and not by the medullary hormones which von Euler has suggested to have primarily metabolic functions.

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Central control of pituitary secretion

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CHAPTER CONTENTS

THE GREEKS BELIEVED that the waste products of a chemical reaction, whereby blood was endowed with 'animal spirits' in the brain, flowed down the funnel-shaped infundibulum to the pituitary gland. From the gland ducts were supposed to pass these waste products into the nasal cavity to form the 'pituita' or nasal mucus. This view was held for many hundreds of years. It is of interest that so far as the pituitary stalk is concerned similar views have been re-expressed in recent years. It is likely that posterior pituitary hormones pass, in some form, down the nerve fibers of the stalk to the neural lobe; and that the anterior lobe of the pituitary is brought under hypothalamic control by means of some humoral agent or agents passing down the portal blood vessels of the stalk to the gland.

ADENOHYPOPHYSIS

Central Nervous System Effects on Anterior Pituitary Activity

The first evidence that the central nervous system might exert a decisive influence on the activity of the anterior pituitary and its target organ glands came from the studies of Marshall (220, 222, 223). He

drew attention to the fact that the sexual rhythms of many birds and mammals are conditioned by changes in the external environment which in all probability affect anterior pituitary activity through the central nervous system. ". . .and it would appear certain that many external factors which regulate the cycle act through the intermediation of the central nervous system upon the anterior pituitary, this gland playing the part of a liaison organ between the nervous system which is affected by stimuli from without and the endocrine system . . ." (222). The basis for such a view was the study of the reproductive cycles of many animals in relationship to a variety of environmental factors such as food, light, temperature, presence of a mate and so on. It was observed (221) that many birds and mammals will show a reversal of the time of the breeding season after transference across the equator. One of the clearest examples of environmental influences on gonadal activity is the effect of variation in environmental lighting. Among the common mammals the reproductive rhythm of the mouse (13, 135), rat (45, 74, 102, 265, 332), ferret (28), hedgehog (1), cotton-tailed rabbit (32), cat (70), raccoon (31), goat (30) and sheep (166, 366) is sensitive to changes in environmental lighting. Of these animals the response of the ferret has been most subjected to experimental study. The optimum light wavelengths (224) and duration of light/dark ratios (145, 167), the necessity of the optic nerves (29, 55), of the hypophysial portal vessels (81), and of the pituitary gland (176) for this response have all been demonstrated. The anestrous state of the female ferret during the months of September to February is most easily changed to estrus if the animals are exposed to 16 hr. of light per day of a wavelength between 6500λ to 3650λ. It seems that the stimulus of light initiates a nervous reflex through the eyes and optic nerves which by some unknown neural pathway excites the adenohypophysis via the pituitary stalk and the resultant discharge of gonadotrophic hormone results in ovarian activity. Many examples could be quoted of similar reactions in birds. There is evidence that the visual and auditory display of other members of a flock may be indispensable to the reproductive activity of individual birds (69). Further the number of eggs laid in a clutch seems to be regulated through either visual stimuli or proprioceptive stimuli from the ventral body surface (see 220). In most birds and some mammals (rabbit, ferret, cat, ground squirrel, short-tailed shrew and mink), the occurrence of ovulation is dependent on coitus or on some form of sexual excitation. For example, the isolated female pigeon does not ovulate, but if the bird is placed in view of a male bird, another female or a mirror, ovulation follows (230). Similarly, in the mammals mentioned above, ovulation is dependent on some stimulus emanating from the male, another female, or mechanical or electrical excitation applied to the vagina or cervix uteri. The mechanism involved is a nervous reflex excitation of gonadotrophic discharge from the pars distalis.

The data relating adrenal cortical activation to environmental change are too well known and numerous to list. The important work of Selye (310, 311) first drew attention to the fact that a constant pattern of response follows the application of many different types of stimuli, the common denominator of which is that they tend to damage, or destroy the homeostasis of, the organism. One element of this 'response to stress' is adrenal cortical activation. For detailed references to the presently accumulated data Selye's publications (312) may be consulted. In the present context it may be mentioned that emotional stress is a potent factor in evoking adrenal cortical discharge, and observations on many forms, including the mouse (80), rat (343), rabbit (57) and especially the human (33, 109, 175, 178, 181, 182, 248), form strong evidence that in some way the central nervous system exerts a controlling influence over the discharge of adrenocorticotrophic hormone (ACTH) from the adenohypophysis.

In the case of the secretion of thyrotrophic hormone (TSH) the evidence is less complete. There is evidence that the overactivity of the thyroid in cases of Graves' disease is secondary to emotional disturbances (40, 59, 77, 122, 144, 210-212, 216, 217, 246, 255), and the idea is often implicit in clinical publications that this thyroid hyperfunction is due to increased secretion of TSH from the pituitary (328). Many workers (38, 46, 242, 256, 356) have reported that emotional and physical stress inhibits thyroid function. It seems clear that in the normal experimental animal emotional stress results in decreased thyroid activity (46).

The above data form strong evidence that the external environment, acting through the central nervous system, may profoundly influence the secretion of the follicle-stimulating, luteinizing, luteotrophic, adrenocorticotrophic and, possibly, thyrotrophic hormones.

Anatomy of Hypothalamoadenohypophysial System

The nomenclature of Rioch *et al.* (284) will be used in discussing anatomical details relating to the

pituitary gland. These authors divide the pituitary into the neurohypophysis ('posterior lobe') and adenohypophysis ('anterior lobe'). The neurohypophysis is subdivided into the three parts of the gland—the median eminence of the tuber cinereum, the infundibular stem and the infundibular process or neural lobe. The adenohypophysis, derived embryologically from Rathke's pouch, is subdivided into the pars distalis, pars tuberalis and pars intermedia. The neural stalk, together with its sheath of portions of the pars glandularis, is designated the hypophysial stalk.

The main secreting portion of the adenohypophysis is the pars distalis and much interest has centered around the anatomical pathway by which the central nervous system influences this part of the gland, and thereby affects also gonadal, thyroidal and adrenocortical function. It has been argued at different times that the pars distalis is controlled by the hypothalamus *a)* by an innervation passing through the peripheral autonomic nervous system (sympathetic fibers from the cervical sympathetic trunk and parasympathetic fibers from the facial nerve), *b)* by a direct innervation passing through the stalk of the gland, *c)* by a systemic blood supply and *d)* by the hypophysial portal blood supply. In view of the embryological origin of the pars distalis from buccal epithelium, and its migration to its final and constant attachment in all vertebrates to the floor of the third ventricle, it would seem teleologically reasonable to suppose that the influence of the hypothalamus was exerted by a direct pathway to the gland.

The first account of any nerves passing to the pituitary gland was a brief mention of a sympathetic supply by Bougery (39) in 1845. Many workers in later years published findings in agreement (for literature see 152), but the comprehensive and more recent studies of Rasmussen (274) and Green (124, 125) fail to lend support to the view that the pars distalis receives a substantial nerve supply of any type. Rasmussen studied the nerve supply to the anterior pituitary in many laboratory animals and found a few sympathetic fibers entering the pars distalis. Since large areas of the gland were found to be free of nerve fibers, the conclusion was drawn that the fibers present were vasomotor in nature. Green (125), in a detailed study of the pituitary gland, in many vertebrates ranging from cyclostomes to man, concluded, "In none of the animals studied has an innervation of the pars distalis been found." One of the difficulties in evaluating early work is due to the capricious nature of silver staining techniques. Such staining methods are likely to impregnate reticular connective tissue fibers as well as nerve fibers (154). Therefore, when such stains have been used (241, 337), accounts of a rich innervation to the pars distalis must be viewed with caution unless rigid control procedures have been applied. Wingstrand (357), investigating the avian pituitary, concludes, "In perfectly impregnated slides in which the reticular fibers are unstained the adenohypophysis contains no or very few nerve fibers." The experimental data regarding the importance of a cervical sympathetic innervation of the pars distalis are clear in its implications. The fact that complete sympathectomy does not prevent normal reproduction in female cats (52) and does not cause any very significant change in the metabolic rate of cats (52) or rats (208) demonstrates that a sympathetic innervation of the pituitary plays no appreciable part in the control of the secretion of gonadotrophic or thyrotrophic hormones. Also pseudopregnancy still follows sterile coitus in the partially sympathectomized rat (112, 340), and ovulation still follows sterile coitus in the partially or completely sympathectomized rabbit (42, 168).

A parasympathetic innervation of the pars distalis was suggested as a possibility by Hinsey & Markee (180). However, again the experimental data argue against such a supply since it has been found that removal of the sphenopalatine ganglia does not result in any reproductive abnormality in the rat (313), and that the normal reflex release of gonadotrophin still follows coitus in the rabbit after bilateral avulsion of the facial nerve (143) and after destruction of the petrosal nerves at the geniculate ganglia (341).

The hypothalamus sends a rich bundle of nerve fibers through the infundibular stem to end in some part of the neurohypophysis. It is probable that a few nerve fibers pass into the pars intermedia and pars tuberalis, but it is doubtful if any penetrate into the pars distalis. Detailed references to the literature on this subject have been given (125, 152, 156, 274). Reports in the older accounts of a rich hypothalamic innervation of the pars distalis are most likely to be explained on silver impregnation of reticular connective tissue fibers. Recent findings with the electron microscope support this view. Electronmicroscopy clearly differentiates between reticular fibers and nerve fibers, and two independent groups (Palay, personal communication; Farquhar, M. G. & J. F. Rinehart, personal communication) have failed to find any nerve fibers in the pars distalis with the use

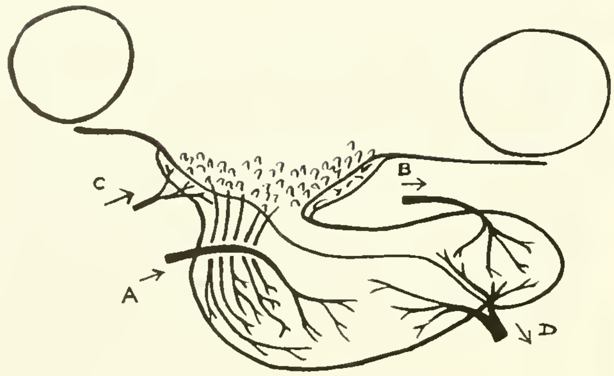

FIG. 1. Diagram of a sagittal section through the pituitary gland (of a rabbit) illustrating the general pattern of blood supply. The anterior and posterior hypophysial arteries, *A* and *B*, are derived from the internal carotid arteries. The arterial twigs, *C*, to the pars tuberalis plexus (which in turn supplies the primary plexus of the portal vessels) are derived from the internal carotid and posterior communicating arteries. The venous drainage, *D*, passes to surrounding venous sinuses in the dura mater or in the basisphenoid bone. [From Harris (156).]

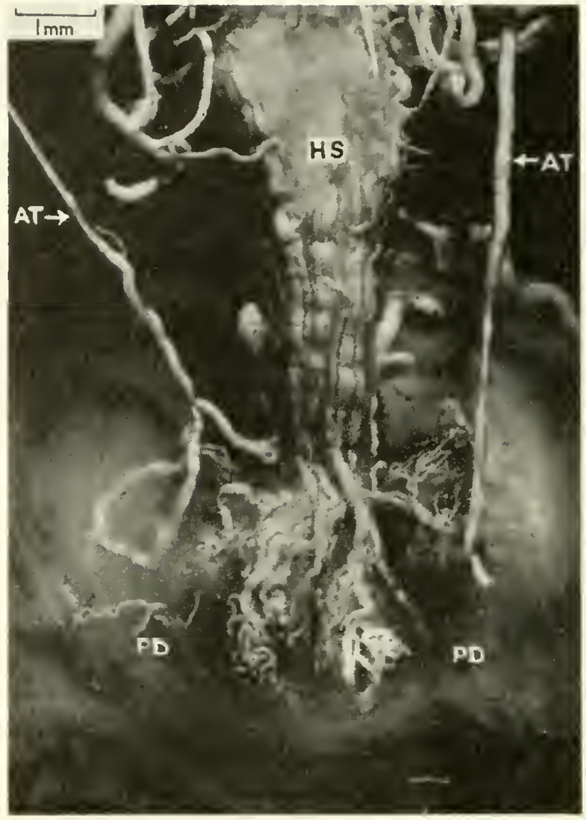

FIG. 2. Photograph of the anterior aspect of the pituitary stalk in man *AT*, artery of the trabecula; *HS*, hypophysial stalk; *PD*, pars distalis. The blood vessels have been injected with neoprene latex. Note the prominent trunks of the portal vessels on the anterior surface of the stalk. These vessels transport blood from the primary plexus, situated in the median eminence of the tuber cinereum above, to the sinusoids of the pars distalis below. (The latter sinusoids have been partly dissected in the substance of the gland.) [From Xuereb *et al.* (365).]

of this technique. The position may be summarized, "The pars distalis of the pituitary may, in general terms, be described as a gland under nervous control but lacking a nerve supply" (152) and, "It is agreed that the anterior pituitary is devoid of secretory nerve fibers and that therefore the mechanisms of secretion must be attributed to humoral factors that reach the gland through its blood supply" (214).

The blood of the pars distalis may be likened to that of the liver in that the gland possesses a systemic arterial supply, a portal blood supply and a systemic venous drainage (fig. 1). The systemic arterial supply appears to be variable in pattern in different forms (see 156). In some animals, such as the rabbit, a definite arterial twig derived from the internal carotid may be traced into the anterior lobe (150) while in other forms, such as the bird (357), rat (205) and human (236, 364), the systemic supply seems to be scanty. However, interruption of the portal vessels has been found to result in only minor degrees of atrophy of the gland (see below) so that it is safe to conclude that a functional systemic supply exists whether it is in the form of capsular capillaries or small arterioles.

The venous drainage of the anterior and posterior lobes of the pituitary is by means of short wide veins draining into surrounding venous sinuses in the dura or in the sphenoid bone. A knowledge of the anatomy of the pituitary venous system, from the gland to the jugular veins, is likely to be of great importance in future years (in attempts to collect pituitary venous blood for direct assay of pituitary trophic hormones) but so far seems to have received little study. In general pattern it would appear to be very variable in different forms.

The hypophysial portal blood supply was first noted by Professor F. I. Rainer of Bucarest and first described in detail by Popa & Fielding (266, 267). These workers described their findings in the human, and were soon confirmed by Wislocki & King (361) and Wislocki (358, 359) and later by Green & Harris (126) and Wingstrand (357) in a variety of animals. This vascular supply of the monkey (359) and man (236, 365) has recently been studied in detail and beautiful reproductions and microphotographs have

been published (see fig. 2). The general nature of the pituitary vascularization is shown in figure 1. The mammalian system consists of small arterial twigs from the internal carotid and posterior communicating arteries which supply a plexus lying between the pars tuberalis and median eminence; from this plexus capillaries or sinusoids of varying shapes and sizes, often in the form of loops, penetrate into the nervous tissue of the median eminence (the primary plexus of the portal vessels) and then drain by the large trunks of the portal vessels which run down the pituitary stalk into the sinusoids of the pars distalis. The phylogenetic constancy of these vessels has been commented upon by Green (125) who examined the pituitary gland in 75 species of vertebrates: "It is a remarkable fact that the hypophysio-portal circulation shows such minor variations between related species and that the variations described can be followed with such ease in so orderly a manner in a phylogenetic series. Such constancy suggests a functional significance. Were it not so, wide variations might be expected to occur, since the general morphology of the pituitary itself is anything but constant." Since the blood in the portal vessels has been seen to flow from the median eminence of the tuber cinereum to the pars distalis of the pituitary in amphibia, mice, rats, cats and dogs (123, 127, 183, 331, 363), the view has been put forward that the hypothalamus may exert its influence over anterior pituitary function through some humoral effect mediated by these vessels. The idea of a humoral control of the adenohypophysis by the hypothalamus or neurohypophysis is not new (see 156, p. 164) but has gained force in the last few years in the light of the above anatomical data and recent experimental findings. There are clearly many possibilities as to how such a mechanism might function, but the most likely seems to be that nerve fibers from the hypothalamus liberate some humoral substance or substances into the capillaries of the primary plexus in the median eminence and that this substance is carried by the portal vessels to excite or inhibit the cells of the pars distalis.

Hypophysial Portal Vessels and Anterior Pituitary Activity

The data that the hypophysial portal vessels are the anatomical structures by which the hypothalamus controls anterior pituitary secretion may be summarized as follows.

a) The hypothalamus exerts an important regulatory effect on adenohypophysial function but the gland lacks a nerve supply. Hinsey & Markee (180), Friedgood (111), Harris (148) and Brooks (43) all suggested, over 20 years ago, that the hypothalamus or neurohypophysis might affect the release of luteinizing hormone from the anterior pituitary by humoral means.

b) The finding that the hypophysial portal vessels formed a constant anatomical link connecting the median eminence of the tuber cinereum with the pars distalis, and that the blood flow in these vessels was from the tuber cinereum to the pituitary, led to the suggestion that any humoral control transmitted to the gland down the pituitary stalk was exerted through these vessels.

c) Electrical stimulation of various regions of the hypothalamus excites gonadotrophic (148, 151, 164, 218), adrenocorticotrophic (72, 188, 271) and thyrotrophic (56, 164) secretion, although similar stimulation of the pituitary gland itself is without effect (72, 151, 164, 218). These data are compatible with the view that the discharge of these hormones is controlled by a neurohumoral mechanism involving hypothalamic neurones (excitable by electrical stimulation) and a humoral mechanism in the pituitary stalk and gland (not excitable by electric stimulation).

d) The discordant findings of different workers regarding anterior lobe function after pituitary stalk section may be explained by varying degrees of regeneration of the portal vessels. Harris (153) first observed such regeneration in the rat and noted that it was correlated with the return of reproductive activity. Regeneration of the portal vessels has now been observed in mice (71), rats (153, 160), rabbits (107, 189), ferrets (81, 329) and monkeys (162), and has been correlated with return of anterior pituitary activity in mice (71), rabbits (107) and ferrets (81).

e) The pituitary gland transplanted to a site in the body remote from the sella turcica shows at most only fragments of normal activity. However, if the glandular tissue is transplanted in a hypophysectomized donor to the sella turcica or to a site in the subarachnoid space below the median eminence (128, 161), then the transplanted tissue may become revascularized by the portal system and apparently normal function returns (161).

The above data show that the hypophysial portal vessels are in some way specifically related to the normal maintenance and regulation of adenohypophysial function. The mechanism by which these vessels exert a controlling influence over the anterior pituitary is not certain. The most likely theory is that

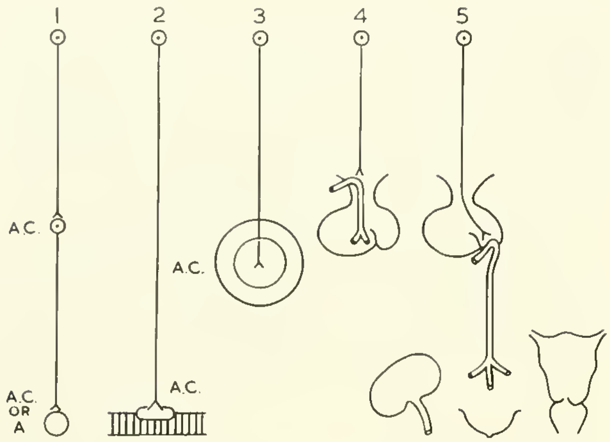

FIG. 3. To compare different systems in which humoral transmission of stimuli may occur. *1*) autonomic nervous system, *2*) neuromuscular ending, *3*) sympathoadrenal medullary ending. In these three systems it is established that a cholinergic (*A.C.*) or adrenergic (*A*) substance is liberated from the nerve terminal and acts directly on the effector cell. *4*) Hypothalamoadenohypophysial system—in which the evidence indicates that a short vascular pathway intervenes between the nerve terminal and effector cell, situated in the anterior pituitary. *5*) Hypothalamoneurohypophysial system—in which a long vascular path (the systemic circulation) intervenes between the nerve terminal in the neural lobe and the effector cells in the kidney, breast or uterus.

the nerve fibers of the hypothalamus liberate some humoral substance or substances into the primary plexus of the portal vessels in the median eminence which is carried to the pars distalis of the pituitary where it exerts a controlling action. However, as has been stated (157), ". . . the neurohumoral view . . . will only be established if it is possible to firstly identify a particular substance which exerts a direct action on anterior pituitary cells; secondly, to show this substance is present in the blood in the hypophysial portal vessels in greater amount than in systemic blood; thirdly, to show that the concentration of this substance in the blood of the hypophysial portal vessels varies according to electrical or reflex activation of hypothalamic nerve tracts; and fourthly, to demonstrate that the activity of the adenohypophysis is correlated with this varying concentration." None of the substances that have so far been investigated may be said to fulfil these criteria. However, the possibility that such substances exist is rendered more likely from what is known regarding chemical transmission in the autonomic nervous system and at the neuromuscular junction, and from present theories regarding neurosecretion and the posterior pituitary gland (see fig. 3). If the above view is correct, then the hypothalamo-adenohypophysial unit would seem to occupy an intermediary position between these other two mechanisms.

HUMORAL STIMULATION OF GONADOTROPHIC SECRETION. Taubenhaus & Soskin (325) were the first to suggest that the release of luteinizing hormone (LH) from the pituitary was controlled by a humoral mechanism acting through the hypophysial portal vessels. Markee *et al.* (219) proposed that an adrenergic mechanism controlled LH secretion. They found that injection of epinephrine into the pituitary gland of rabbits, by means of a parapharyngeal operative approach, resulted in ovulation in a proportion of cases—in 5 out of 10 rabbits following injection of about 100 μg epinephrine (three injections of 40 μl each of 1:1000 solution over the course of 30 min.). Donovan & Harris (82) repeated this work, injecting the gland through a hypodermic needle orientated stereotactically and using a very slow rate of injection (0.0002 ml per min. for 50 to 100 min.). They found 3 out of 16 rabbits ovulated when 60 to 120 μg epinephrine (bitartrate) was injected into the pars distalis, and 0 out of 9 when 60 to 120 μg norepinephrine bitartrate was injected. In an attempt to perfuse the pars distalis more completely with the injected solution, injections were made into the median eminence of the tuber cinereum on the grounds that the solution might diffuse into the primary plexus of the portal vessels and thereby be widely and rapidly distributed in the anterior pituitary. The striking feature of the results of injecting epinephrine and norepinephrine solutions at this site was the progressive reduction in number of positive responses as the rate of injection of the solution was decreased and as the pH of the solution was adjusted to near neutrality. Control injection of isotonic sodium chloride, tartaric acid and acetylcholine also resulted in ovulation in 7 out of 25 cases. It is clear that the correlation of the ovulation response with the chemical structure of substances injected into the tuber cinereum must be made with caution.

Pharmacological blockade of reflexly induced, or spontaneous, ovulation has been studied in an attempt to define a humoral excitant of the anterior pituitary gland. Markee and his co-workers found that various sympatholytic agents blocked coitus-induced ovulation in the rabbit providing they were injected within 90 sec. of the mating act (295, 296). Atropine was also effective in this respect if injected

within 30 sec. of copulation (297). Similarly in rats, the spontaneous ovulation in this form could be blocked by Dibenamine or atropine (95), and by pentobarbital and other barbiturates (94). Ovulation is delayed by 24 to 76 hr. in the cow after atropine administration (146). Estrogens stimulate the release of LH in the rat and if administered to the pregnant animal will result in ovulation. This response may be blocked in a high proportion of cases by Dibenamine or atropine injected prior to, or as much as 20 hr. after, estrogen administration (294). In another form, the hen, ovulation is induced by progesterone (110). This action of progesterone may also be blocked by Dibenamine (336). The site of action of such drugs as atropine, Dibenamine and SKF-501 in blocking ovulation is not clearly established. Markee and his co-workers put forward the suggestion that atropine acts, in this respect, by blocking synaptic transmission in the hypothalamus and that sympatholytic drugs act by blocking an adrenergic mechanism at the portal vessel-pituitary level. The results obtained by the use of such drugs do not point solely in the direction of an adrenergic agent as being the humoral transmitter since Dibenamine possesses some antihistaminic activity (249) and is said to be a powerful antagonist of 5-hydroxytryptamine (91).

Benoit & Assenmacher (23, 32) have produced evidence that a stainable neurosecretory material, originating perhaps in the tuberal nuclei, may play a role in the regulation of gonadotrophic secretion.

HUMORAL STIMULATION OF ACTH, TSH AND LACTOGENIC SECRETION. The most direct data regarding humoral control of ACTH secretion are those reported by Porter & Jones (268). These workers hypophysectomized dogs and collected blood from the empty sella turcica, blood that was derived in part from the upper cut end of the pituitary stalk. The ACTH-releasing potency of this blood was studied by injection into rats pretreated with hydrocortisone. (Such animals were found not to respond to the stress of unilateral adrenalectomy with adrenal ascorbic acid depletion.) Injection of portal vessel blood caused adrenal ascorbic acid depletion in hydrocortisone-inhibited rats but not in hypophysectomized rats, while injection of blood obtained from the carotid artery of the dog did not cause ascorbic acid depletion in either the hydrocortisone-treated or hypophysectomized animal. The conclusion is drawn that some substance is present in blood drawn from the hypophysial portal vessels, but not in carotid artery blood, that evokes ACTH release from the anterior pituitary by a direct action on the gland. Somewhat similar results have been obtained by Schapiro *et al.* (302) who collected blood from the jugular vein of stressed hypophysectomized rats and showed this blood was active in eliciting ACTH release in rats in which a hypothalamic lesion had been placed that blocked a stress response. Porter & Rumsfeld (269) have fractionated portal vessel plasma, and their results indicate that the substance responsible for pituitary activation is either a large protein molecule or is bound to a large protein molecule and is probably not vasopressin.

Some years ago Long and his collaborators suggested that medullary hormones secreted by the adrenal gland might play a part in the stimulation of ACTH release following stressful stimuli. While the medullary hormones may play a role in stress activation of the adrenal cortex in the normal animal, they cannot be regarded as essential to the response since adrenal demedullation has been found by many workers (see 159) not to affect the adrenocorticotrophic effect of stress. However, the above data and the fact that epinephrine has been shown to exert a direct effect on transplanted anterior pituitary tissue (106, 237) raised the possibility of an adrenergic mechanism underlying hypothalamic activation of ACTH release via the portal vessels. Evidence on this point has been obtained with the use of sympatholytic agents. Some of the early investigators reported a partial blockade of the ACTH response to stress by ergotamine (285), Dibenamine (257, 285, 308) and N - (9 - fluorenyl) - N - ethyl - β - chloroethylamine hydrochloride (SKF-501) (298), while in the hands of other workers Dibenamine (104, 326), ergotamine (121) and dihydroergocornin (11) proved ineffective in modifying the stress response. One complication encountered in these studies was the fact that administration of the blockading drug is in itself a nonspecific stress and evokes ACTH discharge. This difficulty has since been overcome by inducing a state of adaptation to the blockading drug by repeated administrations prior to the experiment. Using this technique, Guillemin (136) has shown that treatment of rats with SKF-501 and dibenzyline blocks the release of ACTH consequent to administration of epinephrine or norepinephrine while the adrenal ascorbic acid response to the stress of formalin administration or immobilization is unaltered. These, and similar experiments using Phenergan (138) and atropine (136), militate strongly against the necessary participation of a cholinergic, adrenergic or histaminergic link in hypothalamopituitary activation. One pharmacological

agent which has been found to prevent a stress response on the part of the adrenal cortex is morphine. [See the excellent review of their work by Munson & Briggs (247) and the later confirmatory work of Ohler & Sevy (253).] Morphine effectively blockades the normal response to injection of histamine, epinephrine, vasopressin, surgical trauma and unilateral adrenalectomy. On the likely assumption that morphine exerts its action at some point in the central nervous system, possibly in the hypothalamus, Munson & Briggs argue that these data make it seem unlikely that histamine, epinephrine or vasopressin play any essential part in the normal activation of pituitary ACTH secretion. However it is also possible that morphine acts in some way directly on the pituitary gland. In that case the finding of Ohler & Sevy (253) may be of more physiological significance—that injection of adrenal cortical extract blocks the ACTH response to operative stress and to administration of sympathomimetic amines but, even in large doses, has little effect against vasopressin-induced adrenal ascorbic acid depletion.

In the last few years data have been brought forward relating the hormones of the neurohypophysis to humoral activation of the adenohypophysis. If this is substantiated an obvious correlation would be apparent, from the teleological viewpoint, between the embryological formation of the adenohypophysis and its mode of regulation. The evidence may be summarized as follows.

a) In vitro studies. Pars distalis tissue has been cultured in roller tubes by Guillemin and his coworkers (137, 139–141). They found that such cultures did not release ACTH into the fluid medium after the 8th day of incubation unless explants of the hypothalamus or median eminence were added to the culture. Control tissue in the form of cerebral cortex, liver or spleen was without effect. Data were produced that histamine, acetylcholine, 5-hydroxytryptamine (serotonin), oxytocin, norepinephrine and vasopressin (all known to be present in the hypothalamus) were not the compounds responsible for the effect of hypothalamic tissue (141). However commercial pitressin was active in this respect, although purified arginine-vasopressin was not; therefore the conclusion was drawn that the effect of the commercial extract was due to some fraction extracted with the posterior pituitary hormone (139). Results obtained after fractionation of hypothalamic and crude posterior pituitary extract are in agreement with this view (140). The independent studies of Saffran and his colleagues in Montreal (290–292) are in general agreement. These workers used incubated pituitary and adrenal tissue in a more acute type of experiment and a chemical method for measuring the adrenal corticoids released into the incubation medium. An ACTH-releasing factor was found in posterior pituitary extracts and in vasopressin prepared by the method of Stehle and Fraser. However the ACTH-releasing factor was found to be distinct from vasopressin and oxytocin, and its activity was found to be enhanced by norepinephrine. The active substance has now been isolated by paper chromatography.

b) In vivo studies. McCann & Brobeck (234) have reported that injection of large doses of vasopressin increases adrenocortical activity in the rat. Sayers & Burks (300) and Sayers (299) find that pitressin, extracts of the rat neurohypophysis and du Vigneaud's purified vasopressin increase the blood level of ACTH in the adrenalectomized and anesthetized rat. Pitocin, epinephrine and extracts of spleen, muscle or liver were inactive in this respect. Some experiments on the human (239, 314) have shown that administration of pitressin is more effective in evoking adrenocortical activity than pitocin. Studies of hypothalamic lesions have shown a relationship between the site of lesions which produce diabetes insipidus and those which block ACTH discharge in response to stress (234), and those that prevent compensatory hypertrophy of the adrenal cortex which normally follows unilateral adrenalectomy (113). Martini and his colleagues (227–229) have found that antidiuretic and oxytocic hormones cause signs of adrenal activation when injected into normal, but not hypophysectomized, rats. They obtained evidence that this was a direct effect on pars distalis tissue by experiments utilizing intraocular anterior pituitary transplants.

The possibility that the release of lactogenic hormone from the pars distalis is stimulated by oxytocic hormone has been raised by the observations of Benson & Folley (25). They found that the mammary glands of lactating female rats from which the litters had been removed were maintained in a more active state if repeated injections of oxytocin were given.

A relationship between TSH secretion and posterior pituitary hormone has also been suggested. Dubreuil & Martini (86) have reported that the uptake of radioactive iodine by the thyroid gland of male rats is increased by previous administration of vasopressin, and Harris & Woods (164, 165; unpublished observations) find that electrical stimulation of the hypothalamus in the region of the supraopticohypophysial tract, known to be effective in

releasing posterior pituitary hormone, results in increased thyroid activity (especially in adrenalectomized animals).

c) Studies of neurosecretion. A possible relationship of the neurohypophysis to ACTH release has been discussed by workers studying the neurosecretory material of the hypothalamus and posterior pituitary gland. The fact that stimuli which evoke discharge of ACTH also result in depletion of neurosecretory material, and that neurosecretory material is closely associated with posterior pituitary hormone, has suggested to some workers (244, 254, 287, 303) that this product of the hypothalamohypophysial tract is liberated into the portal vessels and plays the part of a humoral transmitter to the anterior pituitary to excite ACTH release. As mentioned above, Benoit & Assenmacher (22) also associate neurosecretory material with the stimulus to the release of gonadotrophic hormone.

The evidence that neurosecretory material or posterior pituitary hormone is concerned as an intermediary in hypothalamic regulation of anterior pituitary activity is certainly incomplete and equivocal. For example, the *in vitro* studies of Guillemin and of Saffran quoted above show that highly purified preparations of posterior pituitary hormone are not active in causing ACTH discharge. The fact that pitressin is not active in the morphine-treated rat (247) and the results of older studies discussed by Harris (158) would argue against this interesting speculation. More experimental data are clearly required.

Control of Anterior Pituitary Activity

GENERAL PICTURE OF RECIPROCAL RELATIONS BETWEEN CENTRAL NERVOUS SYSTEM AND ENDOCRINE SYSTEM. The central nervous system and the endocrine system are related in a reciprocal fashion (fig. 4). There are many data which indicate that the nervous system regulates the activity of the adenohypophysis and neurohypophysis, and there can be little doubt that the anterior pituitary gland is in turn the major factor responsible for the activity of the testes, ovaries, thyroid and adrenal cortex. On the other hand there is also much evidence of the reverse reaction, that the hormonal secretion of the anterior pituitary target glands react back on to the central nervous system. Two types of effects appear to be mediated. First, to take for example the ovaries, it is well known that a rise in the blood concentration of ovarian hormones exerts an effect, probably on the nervous system, which results in a decreased secretion of gonado-

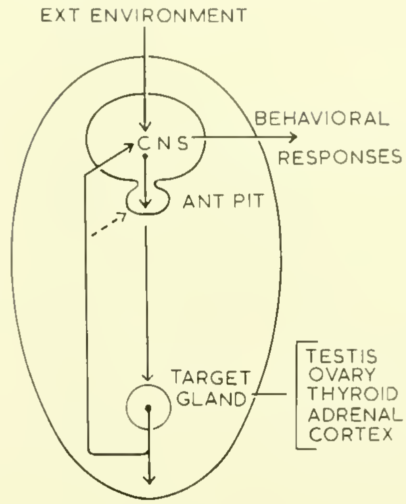

FIG. 4. To illustrate the reciprocal relationship between the central nervous system and endocrine system. The central nervous system mediates the effects of environmental changes, and exerts a regulatory influence over the anterior pituitary gland, which in turn controls the ovary, testis, thyroid and adrenal cortex. The hormones from the latter glands in turn 'feed back' to the central nervous system and pituitary gland to influence *a*) the behavior of the animal and *b*) the activity of the anterior pituitary.

trophic hormone. In this way a type of feed-back mechanism exists, maintaining the pituitary-ovarian activity at a constant level. Second, changes in the blood concentration of the target organ hormones affect the nervous system and thereby overt patterns of behavior. The complicated pattern of courtship, coital and after-play responses of the estrous or estrogenized female cat may be cited (see 14). The effect of varying blood concentration of gonadal hormones on reproductive behavior is dealt with in Chapter XLIX by Sawyer on this subject.

In considering the part played by the central nervous system in maintaining (under constant environmental conditions) and regulating (under conditions of changing environment) the activity of the gonads, thyroid and adrenal cortex, it is necessary to know the activity of the endocrine system at different 'levels': *a*) the autonomous activity of the gonads, thyroid and adrenal cortex in the hypophysectomized animal; and *b*) the activity of the gonads, thyroid and adrenal cortex when anterior pituitary function is autonomous, i.e. the gland is present but isolated from the central nervous system (by pituitary stalk section or pituitary transplantation).

With this background of information it is then

possible to estimate the degree to which endocrine function is dependent on the central nervous system.

ENDOCRINE ACTIVITY AFTER HYPOPHYSECTOMY. It has long been known that hypophysectomized animals survive for longer periods than adrenalectomized, a fact which indicates some adrenal cortical activity on the part of the hypophysectomized preparation. Recent measurements (277) of adrenal activity in the hypophysectomized dog have shown the rate of secretion of aldosterone to be 66 per cent that of control animals, while for 17-hydroxycorticosterone, corticosterone and 11-desoxy-17-hydroxycorticosterone it was only 10 per cent. The thyroid gland retains some slight activity in the absence of the pituitary for the thyroid of the hypophysectomized rat (2, 273) and rabbit (48) still accumulates radioactive iodine and discharges I^{131}-labeled hormone into the blood, although at a low rate. The ovaries and testes appear more wholly dependent on the presence of an intact pituitary, although in some species, such as the rat, the initial stages of oögenesis and spermatogenesis still occur after hypophysectomy (320).

The slight autonomous activity of the adrenal cortex and thyroid shown by the hypophysectomized animal is probably independent of the blood level of adrenal cortical and thyroid hormones. This has been shown for the adrenal cortex by Sayers & Sayers (301) who found the effect of administration of exogenous ACTH on the ascorbic acid concentration of the gland was not modified by administration of adrenal cortical extracts. In the case of the thyroid the position is not so clear. In the hypophysectomized rabbit thyroxine does not affect the rate of release of radioactive hormone from the thyroid (47) nor the response of the gland to administration of exogenous TSH (47, 344). In the hypophysectomized rat thyroxine administration was found (88) to produce no change in thyroid weight, but it has been observed (58) to reduce the thyroid response to exogenous TSH as judged by the criteria of mean thyroid acinar cell heights and the percentage of uptake of I^{131}. However, it is felt that the rate of secretion of radioactive hormone gives a more direct measure of thyroid activity than histological or I^{131}-uptake measurements.

There is no evidence that environmental stimuli can effect the activity of the gonads, adrenal cortex or thyroid in the hypophysectomized animal. It should perhaps be pointed out that the factors regulating the release of aldosterone from the adrenal are not well known. There is evidence that the secretion of this hormone in the dog and rat is not controlled to the same degree by the anterior pituitary as is the secretion of glucocorticoids (96, 97, 277, 286, 316) but may be affected separately by the ionic balance of the blood (286, 317, 342). Another recent view is that aldosterone secretion is controlled by a hormone liberated from the central nervous system and carried to the adrenal in the general circulation (276). It is possible that the release of this hormone could be affected in the absence of the pituitary.

ANTERIOR PITUITARY ACTIVITY AFTER PITUITARY STALK SECTION OR TRANSPLANTATION. Section of the pituitary stalk interrupts the hypophysial portal blood vessels. It has now been established that after simple stalk section this system of vessels regenerates across the site of section in the majority of animals [mouse (71), rat (153, 160), rabbit (47, 50, 107, 189), ferret (81, 329) and monkey (162)]. Further, if stalk section with plate insertion is performed, a capillary plexus may in some cases form in the fibrous capsule of the plate and so re-establish at least slight vascular continuity between the median eminence and adenohypophysis (107, 345). If the plate is slightly misplaced then larger vessels may rejoin the stalk ends around the borders of the plate (81, 153).

Most workers are agreed that section of the hypophysial stalk interferes with anterior pituitary function in a large number of cases. Two views have been put forward in explanation. First, that stalk section decreases the blood supply of the anterior pituitary to a sufficient extent to result in ischemic atrophy and thereby loss of function of the gland. Second, that stalk section deprives the anterior lobe of some specific physiological stimulus, emanating from the hypothalamus and transmitted through the portal vessels, which is necessary for the normal activity of the gland.

To estimate the significance of adenohypophysial atrophy after cutting the stalk it is necessary to measure the volume of the pars distalis rather than that of the whole pituitary. Section of the pituitary stalk in the rat is followed by a slight and variable area of necrosis in the center of the pars distalis. This butterfly-shaped (in transverse section) area has been observed after extensive electrolytic lesions in the median eminence (Dumont, S., personal communication) and has been depicted and described after stalk section (354) and after cautery of the portal vessels of the rat pituitary stalk (67). Similar central necrosis has been observed in amphibians (207), birds (22, 315), sheep (68) and humans (288; Ehni, G., personal communication). Some figures are available for the amount of pars distalis tissue, well vascularized

TABLE 1. *Volumes of the Whole Pituitary Gland, and of Its Different Lobes in Rabbits Submitted to Simple Stalk Section, and Stalk Section with the Insertion of a Plate Between the Cut Ends*

	Whole Gland	Pars Distalis	Pars Intermedia	Neural Lobe	Median Eminence
Normals (21)	100.0±4.3*	100.0±5.6	100.0±6.9	100.0±4.6	100.0±6.2
Simple stalk section (12)	62.4±2.9	67.5±3.9	100.8±8.1	26.6±2.1	150.8±13.8
Stalk section with a plate (28)	73.8±4.2	82.9±5.4	110.8+7.3	25.7±1.6	206.2±10.8

Volumes for normal rabbits expressed as 100%.
Number in parentheses represents number of animals in group.
* Standard error of mean.

Data from Campbell & Harris (50)

and well maintained, several weeks or months after cutting the stalk. The pars distalis of the drake atrophies to about 70 per cent of normal volume after cutting the hypophysial portal vessels (tractotomy) (22), and that of the ferret shrinks to 80 to 95 per cent of normal volume (81). More detailed measurements have been made in the rabbit (50), the results of which are given in table 1. In this form the pars distalis atrophies to about three quarters of normal size. In considering whether the functional deficiencies of the pars distalis produced by stalk section are consequent upon this degree of ischemic necrosis and atrophy, two points arise. *a)* The same degree of atrophy of the pars distalis occurs in the ferret (81) and rabbit (50), and probably in the rat (153), whether the stalk is simply sectioned or is cut and a plate inserted between the cut ends. However, loss of anterior pituitary function is marked and constant only in animals in which a plate has been correctly inserted between the stalk ends and is not detectable in many animals following simple stalk section. *b)* Studies of the functional loss following varying degrees of incomplete hypophysectomy (118, 197, 198, 282, 321, 349) show that about 30 per cent of the normal volume of the pars distalis is sufficient to maintain normal anterior pituitary function, that 10 per cent will maintain some gonadotrophic activity and may result in only minor degrees of adrenocorticotrophic and thyrotrophic deficiency, and that some adrenocorticotrophic function persists unless hypophysectomy is complete. From the above data it seems clear that anterior pituitary deficiency following stalk section is not due to ischemic atrophy but is probably due to interruption of some specific physiological stimulus to the gland derived from the hypothalamus.

Gonadotrophic Secretion After Pituitary Stalk Section or Transplantation. Early studies on the effect of pituitary stalk section have been reviewed (156). It is sufficient to give here as an example some of the work reported on one species, the rat. In this form section of the hypophysial stalk was found to result in lengthened estrous cycles (44, 280), in gonadal atrophy in male and female animals (41, 350, 351), and in normal, lengthened or absent estrous cycles (74, 75). Similar discordant results could be quoted in other forms including the guinea pig, rabbit and dog. In 1950 it was suggested (153) that a possible reason for the discrepancies in these reports might lie in varying amounts of regeneration of the hypophysial portal vessels across the site of stalk section. To test this idea Harris (153) cut the pituitary stalk by a temporal approach in 53 female rats and found that the portal vessels in the rat may regenerate rapidly across the site of section and that the reproductive capacity of the animals could be correlated with such vascular regeneration. Greep & Barrnett (129) and Barrnett & Greep (16) have studied the effects of pituitary stalk section in male and female rats, but since the parapharyngeal route was used to section the stalk the final microscopic study of the region was complicated by the presence of scar tissue and adherence of the structures to the drill hole in the base of the skull. Recent studies have been made in other forms such as the duck, ferret and rabbit. Benoit & Assenmacher, after a preliminary study of the anatomy and blood supply of the duck pituitary (20), devised an operative approach to the pituitary region which allowed them to make a lesion in the anterior part of the median eminence (*eminentiotomie*), to cut the portal vessels of the pituitary stalk and place a plate of sclera at the site of section (*tractotomie*) or to cut the nerve fibers of the stalk (*mischotomie*). The former two procedures were found to result in atrophic testes and the last procedure to have no effect on the normal development of the testes (9, 10, 21–23). These beautiful experiments on the duck have made possible then a differentiation between the importance of the nerv-

ous and vascular components of the stalk for gonadotrophic secretion. Shirley & Nalbandov (315) have obtained similar results in the hen. Donovan & Harris (81) observed that stalk section in the ferret was followed by the development of light-induced estrus if regeneration of the hypophysial portal vessels was allowed to occur. If such regeneration was prevented no estrous response to light was seen and the reproductive organs were found to be atrophic. There was no difference in size or vascularity of the pituitary gland in the two groups. Thomson & Zuckerman (329) had previously found that regeneration of the portal vessels may occur in the ferret but thought that such regeneration was not necessary for the light-induced estrous response. Fortier *et al.* (107) studied rabbits after pituitary stalk section. Again, those animals with well-marked portal vessel regeneration showed normal ovaries and some accepted the male and ovulated. The group in which vascular regeneration was nearly or completely prevented had ovaries and reproductive tracts indistinguishable from the hypophysectomized control group. The volumes of the pituitary glands in these two stalk-sectioned groups were not significantly different (table 1). From the above results it may be concluded that the central nervous system, acting via the hypophysial portal vessels, *a*) maintains gonadotrophic secretion at its normal level (as demonstrated by ovarian weight and size, the onset and maintenance of estrus in the ferret and rabbit, and the cycles of estrus in the rat), since if the pituitary stalk is effectively cut no demonstrable secretion of gonadotrophic hormone occurs (i.e. the reproductive organs are indistinguishable from those of hypophysectomized animals); and *b*) mediates reflex changes in gonadotrophic secretion dependent on environmental stimuli (light-induced estrus in the ferret, the pseudopregnancy response to sterile coitus in the rat and the ovulatory response after coitus in the rabbit).

The functional activity of the adenohypophysis is very markedly reduced if it is transplanted to a site in the body remote from its normal position, and in this respect the anterior pituitary differs sharply from the gonads, thyroid and adrenal cortex. The evidence for this statement has been recently reviewed (23, 156). Although some gonadotrophic activity was ascribed to pars distalis tissue placed in the testis, anterior chamber of the eye, thigh muscle and other sites in several earlier studies (177, 231, 232, 260, 304, 305), the methods that were used for checking the completeness of the initial hypophysectomy must be held open to doubt. More recent workers among whom may be mentioned Westman & Jacobsohn (353), Greer *et al.* (134), Cheng *et al.* (54), McDermott *et al.* (237), Fortier (105) and Harris & Jacobsohn (161) have all reported that gonadal atrophy follows transplantation of the pituitary gland to a site remote from the sella turcica. The most convincing evidence that pituitary tissue, isolated from the influence of the hypothalamus, still possesses some residual gonadotrophic activity comes from the experiments of Everett (92, 93) who made autotransplants of the pituitary into the kidney of the rat and found evidence for some secretion of luteotrophic hormone but not of follicle-stimulating or luteinizing hormone. The question then arises as to the cause of the difference in functional ability of transplants of the gonads, thyroid and adrenal cortex as compared with that of anterior pituitary transplants. One possible explanation appeared to be that gonadal, thyroidal or adrenal cortical tissue would receive its physiological stimulus (in the form of gonadotrophic, thyrotrophic or adrenocorticotrophic hormone) via the general circulation wherever it was placed in the body. On the other hand if anterior pituitary tissue is normally activated by some humoral stimulus passing to the gland by the hypophysial portal circulation, then if the gland is transplanted away from the site of these particular vessels a loss of activity might be expected. This view was put to the test by Harris & Jacobsohn (161) who grafted anterior pituitary tissue, in hypophysectomized rats, either on to the surface of the temporal lobe of the brain, where it became vascularized by the cortical vessels of the cerebrum, or on to the tuber cinereum of the hypothalamus, where it became vascularized by the hypophysial portal vessels (fig. 5). In the case of the temporal lobe grafts, no estrous cycles were observed and post mortem the ovaries and reproductive tracts were found to be completely atrophic. In contrast were the findings in the animals with grafts under the tuber cinereum in which normal reproductive activity (including regular estrous cycles, pregnancy and lactation) was observed to return in a large proportion of cases. It was concluded from these experiments that good vascularization irrespective of the source of the blood is not sufficient to render anterior lobe tissue functional; some additional factor is necessary and this factor is present when the blood supply is derived, at least in part, from the hypophysial portal system.

The study of pituitary grafts placed under the tuber cinereum of hypophysectomized recipients (161) furnished some data on two further points of interest

with regard to hypothalamic control of the adenohypophysis.

a) Lack of sexual differentiation of anterior pituitary tissue. Gonadotrophic secretion in most female mammals occurs cyclically while in the corresponding males a steady level of secretion probably obtains. If ovarian tissue is transplanted into castrate male rats, follicular ripening occurs; but the cycles of ovulation and luteinization have rarely been seen. This is generally taken to indicate a relative lack of secretion of luteinizing hormone by the male pituitary and thought to indicate a sexual differentiation of pituitary tissue. That this conclusion is not true may be seen from the fact that male pituitary tissue grafted under the tuber cinereum of hypophysectomized female rats is capable of maintaining normal estrous cycles and pregnancy in the female hosts (161, 226). Therefore the rhythm of gonadotrophic secretion in the female seems to be dependent neither on the presence of ovaries nor on the presence of a genetically female pituitary gland. It seems likely that anterior pituitary tissue remains pluripotential in its functional capacity and that its pattern of activity in the male or female depends on a stimulus derived from the (male or female) hypothalamus.

b) Onset of puberty. It has long been known that ovaries obtained from immature donors and transplanted into ovariectomized adult females show hastened development. In a somewhat similar fashion it has now been shown (161) that pituitary tissue taken from newborn rats and grafted under the tuber cinereum of adult hypophysectomized females can support adult female reproductive activity long before the donor animals would have reached puberty. Thus the onset of puberty cannot be attributed solely to aging of ovarian or pituitary tissue and is probably dependent on maturation of some neural mechanism, the site of which may be in the hypothalamus. This view is reinforced by those cases of precocious puberty in the human which are associated with small localized tumors of the hypothalamus (see 19, 347), and the fact that hypothalamic lesions may hasten the onset of puberty in young rats (84).

Adrenocorticotrophic Secretion After Pituitary Stalk Section or Transplantation. As first pointed out by Selye (310, 311) the release of ACTH from the anterior pituitary is induced by a great variety of stimuli and represents a common response to the adverse changes of the environment which have been grouped under the term 'stressors.' Most studies of pituitary stalk section have been made to see whether the procedure affects the adrenal cortical response to stressful stimuli. In

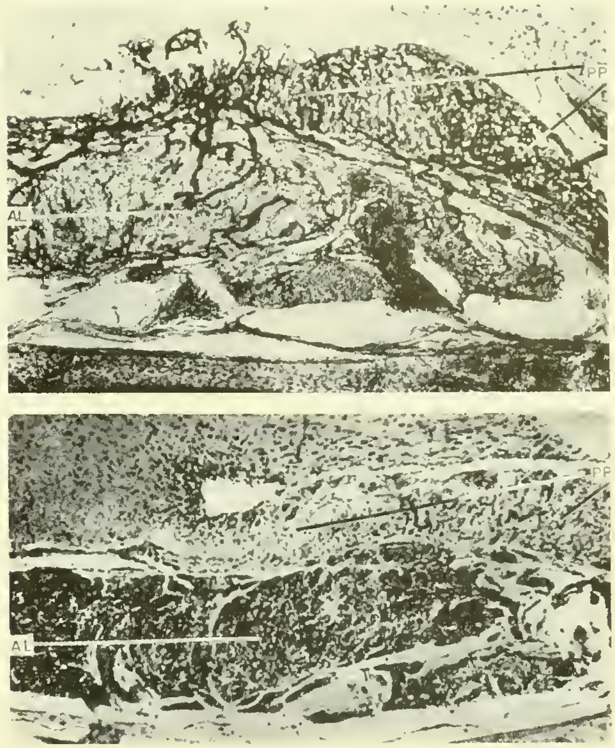

FIG. 5. Microphotographs of sagittal sections through the hypothalamus, a pituitary graft and base of skull of a rat. $\times$ 42 *Upper:* An unstained section 100 μ thick. Note the vascular connections passing from the primary plexus (*P.P.*) of the hypophysial portal vessels to the graft (*A.L.*). India ink injected specimen. *Lower:* An adjacent section through the same specimen as illustrated in *upper portion.* To show the graft, consisting of anterior lobe tissue (*A.L.*). *P.P.*, primary plexus. 10 μ thick. Hematoxylin and eosin. [From Harris & Jacobsohn (161).]

the hands of earlier workers stalk section was generally found not to prevent this response. Uotila (333) reported that adrenal enlargement consequent to cold exposure was not prevented in the rat by section of the pituitary stalk. Similarly this procedure failed to prevent the adrenal hypertrophy elicited by cold in the rat (17) and dog (197), the cold-induced adrenal cholesterol depletion in the guinea pig (324), and the adrenal ascorbic acid response to injection of histamine (53) or surgical trauma (108) in the rat. However, it has since been shown that regeneration of the hypophysial portal vessels may occur across the site of pituitary stalk section. Among later workers who have taken this factor into account may be mentioned the following. Hume (184) placed a polythene sheet between the cut ends of the stalk in the dog and observed, nevertheless, a normal eosino-

penic response to operative trauma or injection of epinephrine. However since a detailed histological study was not made the author concluded: "It cannot be conclusively stated that the hypophysial vessels had not regrown." De Groot & Harris (72) observed that electrolytic lesions placed in the path of the portal vessels (in the zona tuberalis of the pituitary gland of the rabbit) abolished the lymphopenia that follows emotional stress, although lesions of a similar nature in the center of the gland had no effect. In a further study on stalk-sectioned mice de Groot (71) found that those animals in which portal vessel regeneration occurred showed a return of the stress response after operation, whereas the animals in which a plate had been placed between the ends of the stalk showed loss of the adrenal response to stress for the duration of the experiment and adrenal atrophy. McCann (233) reported that the eosinopenia induced by epinephrine and the adrenal ascorbic acid response to unilateral adrenalectomy were prevented in the rat by extensive electrolytic destruction of the pituitary stalk. Donovan & Harris (81) studied the adrenal weights of ferrets with cut stalks under normal environmental conditions. Animals in which portal vessel regeneration had been prevented showed a significant loss of adrenal weight, whereas animals in which vascular regeneration occurred across the site of section showed no adrenal atrophy. This finding was taken to indicate a reduction in the basal rate of ACTH secretion under nonstress conditions following interruption of the portal vessels. In the study of Fortier *et al.* (107) on the rabbit, marked adrenal atrophy was found to follow stalk section (although not to the extent seen in hypophysectomized controls), whether portal vessel regeneration occurred or not. The responses to stressful stimuli were however different in the two groups in that the animals in which vascular regeneration was prevented failed to respond to stimuli calculated to give rise to predominantly nervous or emotional excitation (restraint, exposure to cold), although they did respond to stimuli involving tissue trauma or metabolic disturbances (laparotomy, injection of epinephrine). Recently Hume (186) has made observations on the monkey in which the pituitary stalk had been cut and a film of polythene placed between the hypothalamus and pituitary gland. In these animals the release of ACTH in response to operative trauma 1 to 3 mo. after stalk section was markedly decreased though not entirely prevented.

The results of studies utilizing the method of pituitary transplantation are more clear-cut than those using pituitary stalk section, perhaps because the complete absence of hypophysial portal vessel regeneration can be established with more certainty. As a preliminary to the data mentioned below, it may be said that if pituitary tissue is grafted in the hypophysectomized rat under the median eminence of the tuber cinereum, then adrenal glands within the normal weight range are maintained (161). These pituitary grafts were found to be vascularized by vessels derived from the primary plexus of the hypophysial portal system. In contrast to this finding are the results of studies in which pituitary tissue is transplanted to a site outside the reach of the portal vessels. Such grafts have been found by many different workers (54, 105, 161, 237, 238, 260, 306, 353) to be incapable of maintaining normal adrenal weights, and in most reports the adrenals are markedly atrophic although slightly larger than in hypophysectomized controls. The ACTH response of pituitary transplants to the effect of stress stimuli has been studied by many groups. Cheng *et al.* (54) showed that the combined stress of unilateral adrenalectomy and histamine injection resulted in a fall in adrenal ascorbic acid concentration in pituitary transplanted rats. Fortier & Selye (108) obtained the same result in rats following unilateral adrenalectomy and exposure to cold. The subcutaneous injection of epinephrine, or even of hypertonic saline, was reputed to produce a significant fall of the blood eosinophiles in pituitary transplanted animals (237). In 1951 Fortier (105) made the significant observation that the ability of transplants to release ACTH in response to stressful stimuli depended on the type of stimulation used. He found that hypophysectomized rats bearing intraocular transplants, while still showing an eosinopenic response to so-called systemic stimuli (cold, administration of epinephrine or histamine), failed to give any evidence of ACTH release in response to neurotropic stimuli (nervous or emotional stimuli, such as intense sound or immobilization on a board). It was suggested that the hypothalamohypophysial pathways are required for pituitary activation in response to stimuli acting via the central nervous system, whereas the corticotrophic effect of systemic stress is mediated through changes in the composition of the blood in the general circulation, acting either independently or concurrently on the pituitary to elicit the discharge of ACTH.

Thyrotrophic Secretion After Pituitary Stalk Section or Transplantation. Pituitary stalk-sectioned rats were found by Uotila (333) to possess thyroid glands that were histologically normal. However, lack of good

control procedures for assessing hypophysial portal vessel regeneration left the finding open to doubt, and especially since several workers (17, 352, 355) found that stalk section results in histological signs of thyroid atrophy. More recently it has been observed (81) that effective stalk section (with little or no portal vessel regeneration) results in a 4-hr. thyroidal uptake of I^{131} in the ferret of about one-third normal, although stalk section which was followed by obvious portal vessel regeneration did not decrease the uptake below normal. Less valid criteria for assessing the absolute level of thyroid activity (48-hr. uptake of I^{131} and rate of release of hormonal radioactivity from the thyroid) gave much the same result in the rabbit (47). These results indicate that effective stalk section results in a reduction of the basal level of thyroid activity although not to that seen in the hypophysectomized animal, and that it is interruption of the portal vessels of the stalk that is responsible for this effect. Now, since in recent years it has become apparent that various noxious stimuli inhibit the activity of the thyroid gland (46), it became of interest to see the effect of pituitary stalk section on this stress response. In a study performed on rabbits Brown-Grant *et al.* (47) found that the operation of stalk section with plate insertion largely abolished the thyroid inhibition to restraint but had little effect on the inhibition following laparotomy. In simply stalk-sectioned rabbits the thyroid response to restraint was still present in 11 out of 12 animals and these rabbits were found, post-mortem, to possess regeneration of the portal vessels. These findings are consistent with the hypothesis of Fortier (105) regarding the dual control of ACTH release. In the same work it was found that injection of thyroxine still inhibits the secretion of TSH in the absence of anatomical connections between the hypothalamus and pituitary, thus indicating that a direct action of thyroid hormone on anterior pituitary cells is involved in the feed-back mechanism (see below).

Transplants of pituitary tissue under the median eminence of the tuber cinereum were found to maintain the thyroid in a normal state, as judged histologically (161). In these cases the pituitary grafts were vascularized by the hypophysial portal system (see fig. 5), but in control animals in which the grafts were placed in the subarachnoid space, outside the range of the portal vessels, thyroid atrophy occurred. This latter finding has been the usual experience of workers who have studied the thyrotrophic activity of pituitary tissue transplanted to a site remote from the sella turcica. Schweizer & Long (307) found intra-ocular transplants of the anterior pituitary maintained some thyrotrophic activity in a few of their animals but at a greatly reduced level. Greer *et al.* (134) observed that pituitary transplants in hypophysectomized mice did not maintain the weight of the thyroid above that of hypophysectomized controls but that the uptake of I^{131} per unit thyroid weight and the thyroid-serum iodide ratio was two thirds the level of the intact controls. von Euler & Holmgren (345), working on hypophysectomized rabbits bearing pituitary transplants, found thyroid activity was reduced, although it was higher than in hypophysectomized control animals. They found further that the thyrotrophic activity of the pituitary transplants was no longer modified by exposure to cold, or by anesthesia, but was still inhibited by injection of thyroxine. These workers confirmed the finding that thyroxine may exert an effect directly on the pituitary gland by injecting minute amounts of thyroxine into the gland in normal rabbits (344).

In summary, it may be said that the anterior pituitary gland, disconnected from the central nervous system, still maintains a residual secretion of TSH and that this secretion may be inhibited by a raised blood level of thyroxine or by stress stimuli which involve tissue damage or cause a raised blood level of adrenal steroids. The effects exerted by the nervous system over TSH secretion would appear to be to maintain the normal rate of secretion and to modify this rate in response to stimuli acting through the central nervous system.

Lactogenic Hormone Secretion After Pituitary Stalk Section or Transplantation. The nervous system may be related to lactation in two ways. First, it is well established now that the stimulus of suckling, and the conditioned reflexes that may be associated with this process, evokes nervous reflex release of oxytocic hormone and that this hormone causes contraction of the myoepithelial cells of mammary tissue and so a positive milk ejection from the breast to the young. Second, as first suggested by Selye (309), the nervous stimulation of suckling may be of importance in maintaining secretion of the lactogenic hormone and thereby milk secretion. Both the neurohypophysis and adenohypophysis may therefore exert an individual and specific action on mammary tissue. It is possible that the two lobes of the pituitary are interrelated in lactation in yet a further way since Benson & Folley (25) have found that the mammary glands of lactating female rats, from which the litters had been removed, were maintained in a more active state if repeated injections of oxytocin were given. Oxytocin

released from the neurohypophysis may stimulate the secretion of lactogenic hormone from the pars distalis. Any experiment designed to analyze the role of the hypothalamus in lactation must then take cognizance of this possibility as well as the fact that hormones from both lobes of the hypophysis are involved in normal mammary function. Since the above information is of recent origin, it is clear that the results of many older studies require re-evaluation.

The effect of pituitary stalk section on the secretion of the lactogenic hormone is not clear. It has been found that stalk section in lactating rats causes failure of lactation in spite of functioning anterior pituitary tissue and continued suckling (76, 173), results in death of the young and mammary involution, although not to the degree as seen after hypophysectomy (190), and may be followed by normal lactation (75). Dandy (65) described a case of stalk section in a young woman that was followed by normal menstrual cycles, pregnancy, labor and lactation. Since stalk section may leave intact 10 per cent or more of neurohypophysial tissue in the upper part of the stalk and in the tuber cinereum, and since portal vessel regeneration may occur to the pars distalis, the interpretation of these results is open to doubt. A somewhat clearer situation was found in hypophysectomized female rats bearing pituitary grafts beneath the median eminence of the tuber cinereum (161). As described above, these animals showed normal estrous cycles, mated and became pregnant, and delivered living young. However, in spite of obvious distension of the mammary glands with milk, the young died from starvation unless the maternal rat received repeated injections of oxytocic hormone after which they survived and grew In these transplanted animals then there existed a posterior pituitary deficiency with failure of the milk-ejection reflex. Oxytocic replacement therapy revealed, however, that anterior pituitary tissue grafted on to the median eminence is capable of maintaining milk secretion. Unfortunately the extent to which pituitary transplants remote from the sella turcica support lactation is not known since animals with such transplants do not show estrous cycles or become pregnant.

TARGET GLAND ACTIVITY AFTER HYPOTHALAMIC LESIONS. The fact that hypothalamic lesions may result in endocrine disturbances has been known since Camus & Roussy (51), Bailey & Bremer (12) and Smith (319) noted genital atrophy following damage to this area of the brain. Later studies, using more precise stereotaxic methods, have shown that large lesions in the tuberal region of the hypothalamus, which interrupt all hypothalamohypophysial connections, produce the same effects on pituitary function as does complete and permanent stalk section. (The one exception to this statement is the effect of these procedures on stress-stimulated release of ACTH as described below.) Smaller and more localized lesions, placed bilaterally, produce differential effects on the secretion of various pituitary hormones.

Gonadotrophic Secretion and Hypothalamic Lesions. Gonadal atrophy has been observed to follow hypothalamic lesions by many workers. One of the more detailed studies is that reported by Dey and his coworkers in a series of papers (see 78) in which they studied the effect of such lesions on the estrous cycle of guinea pigs. Loss of cyclical phenomena and genital atrophy were found to follow lesions at the junction of the hypothalamus and pituitary stalk. Sexual atrophy in association with lesions of the tuber cinereum has been observed in rats (35, 174, 233, 240), dogs (26), rabbits (322) and cats (206). The production of gonadal atrophy however, may not be a highly significant response in view of the fact that dietary deficiency, metabolic upset and other general disturbances could possibly give rise to the same phenomena, indirectly.

A state of persistent estrus after the placement of hypothalamic lesions has been reported in the guinea pig and rat (3, 4, 18, 78, 132, 179). Most authors agree the effective site for the production of this effect, viz. the abolition of the rhythmic release of LH and the constant secretion of FSH, lies behind the optic chiasma in the region of the paraventricular nuclei. These results cannot be attributed simply to the destruction of an LH-controlling 'center', for Greer (132) found that the injection of small daily doses of progesterone was followed by a resumption of 4- to 6-day vaginal cycles. Similarly, electrical stimulation or caging with a male may also be followed by a diestrous interval in such persistent estrous animals.

A recent and striking finding has been the production of FSH secretion after placing lesions in the anterior hypothalamus (83). In this study bilateral lesions were placed behind the optic chiasma in female ferrets at a time of year when the normal animal would be anestrous. Within 3 to 7 weeks, 11 out of 18 animals were in full estrus. Since prolonged electrical stimulation of the hypothalamus failed to elicit the same result, the response is probably due to destruction of a hypothalamic region which normally exerts an inhibitory influence over FSH secretion. These results seem in several ways similar to those

obtained by Flerko (103), and to those observed in young children who develop hypothalamic tumors and precocious puberty. The literature on these latter cases is reviewed by Weinberger & Grant (347) and Bauer (19). The experimental production of premature secretion of FSH, and precocious puberty, by damage to the hypothalamus has been observed by Gaupp (119) in the rabbit and Donovan & van der Werff ten Bosch (84) in the rat. One puzzling finding of these results is that lesions in the anterior hypothalamus (84) seem responsible for the release of FSH secretion in the experimental animal, whereas the general finding in clinical studies is that tumors in the region of the mammillary bodies are more often associated with pubertas praecox in the human. It may be anticipated that this important field will receive much attention in the next few years.

ACTH Secretion and Hypothalamic Lesions. There is good evidence that hypothalamic lesions will markedly reduce, or abolish, the increased discharge of ACTH that normally follows conditions of stress. de Groot & Harris (72) found that bilateral electrolytic lesions in the posterior part of the tuber cinereum or in the mammillary body might abolish the lymphopenia produced by emotional stress in rabbits, and Hume & Wittenstein (188) found that the eosinopenia following stress in dogs was prevented by paramedian lesions in the anterior hypothalamus. Hume (185, 186) has more recently reported that lesions in the anterior part of the median eminence are most effective in abolishing the ACTH response to stress. Confirmatory results have been obtained in other forms, such as rats (6, 90, 233, 318), cats (206, 270) and monkeys (271).

a) Lesions and resting rate of ACTH secretion. Hypothalamic lesions have been reported as having little effect on adrenal size (116, 206, 233) although the stress-induced release of ACTH was blocked in some animals. This would indicate that hypothalamic lesions do not affect the resting rate of secretion of ACTH. However, adrenal atrophy following hypothalamic damage has been seen in a few animals (36) and was reported (234) to follow interruption of the supraopticohypophysial tract in rats in which the water intake per day was increased to 100 to 200 ml. Greer & Erwin (133) have recently reported that some adrenal atrophy occurs in the rat after lesions of the median eminence. Since gonadal and thyroidal atrophy may follow hypothalamic lesions it would be somewhat surprising if further observations showed normal adrenals in the presence of similar lesions.

b) Types of stress. Destruction of areas in the median eminence or posterior tuber cinereum has been found to abolish the stress response to epinephrine, surgical trauma or unilateral adrenalectomy (116, 187, 233, 270, 271). These findings are in apparent conflict with the observations that complete separation of the pituitary from the hypothalamus, by stalk section or transplantation, is compatible with ACTH responses to the same stimuli. A possible explanation has been suggested by McCann (233). "A neurohumoral substance is released in the median eminence which normally traverses the hypophysial portal vessels and causes release of ACTH. In cases of severe stress, sufficient amounts of this substance may be released to activate the anterior lobe via the general circulation." On this view the response of the transplanted or stalk-cut pituitary would not depend on the nature but on the relative intensity of the stress stimuli which would in all cases act through the hypothalamus.

c) Site of effective lesions. There is no general agreement as to the site of lesions which result in blockade of the ACTH discharge following stress. Some workers place the effective site in the posterior tuber cinereum and mammillary region (72, 90, 270, 271, 318) while others give the effective site as median eminence (206), anterior median eminence (186, 187) or in the path of the supraopticohypophysial tract (234, 235). Such discrepancies as these are perhaps not surprising in view of the complex, and largely unknown, anatomy of the tracts in the hypothalamus and the fact that many nervous reflex paths may initiate the ACTH response to different types of stress stimuli.

d) 'Feed-back' mechanism. It is well known that an increased blood level of adrenal steroids inhibits ACTH secretion and a decreased blood level (after unilateral adrenalectomy) stimulates ACTH secretion. Ganong & Hume (116) on dogs and Fulford & McCann (113) on rats have both shown that the compensatory hypertrophy after unilateral adrenalectomy is abolished by lesions in the anterior median eminence. However, Ganong & Hume (117) found that median eminence destruction in the dog did not prevent adrenal atrophy following administration of cortisone. It is of interest that these superficially discordant findings are similar to those regarding the feed-back mechanism of thyroid hormone (see below).

TSH Secretion and Hypothalamic Lesions. Many workers have now reported that lesions in the hypothalamus may interfere with the normal secretion of TSH (35, 36, 66, 115, 130, 131, 133, 278).

a) Lesions and resting rate of TSH secretion. There can be little doubt that the normal resting rate of secretion of TSH is reduced by lesions in the anterior hypo-

thalamus. Greer (130) found the thyroid glands of rats with such lesions (even treated with propylthiouracil) to be slightly smaller than untreated controls. Bogdanove *et al.* (36) found that hypothalamic lesions in rats resulted, in a few cases, in thyroid atrophy. Ganong *et al.* (115) reported that in 5 out of 23 dogs hypothalamic lesions resulted in a reduction in I^{131} uptake by the thyroid and histological signs of thyroid atrophy. These five animals were found to possess lesions in the anterior end of the median eminence. More recently D'Angelo & Traum (66) have demonstrated both a thyroid atrophy, and a reduction (to about one-half normal) of the TSH concentration in the blood, following anterior hypothalamic lesions in rats. It seems clear that the reduction of thyroid activity is not as great as that following hypophysectomy which confirms the results discussed above obtained by pituitary stalk section.

b) Site of effective lesions. There is general agreement that the effective site lies in the anterior hypothalamus. Greer (130) states, "The impression gained so far, however, is that the area is anterior to the ventromedian nucleus and lies along or near the ventral surface of the hypothalamus, possibly near the ventral extension of the supraopticohypophysial tract." This site has been confirmed in rats (35) and dogs (115).

c) 'Feed-back' mechanism of thyroid hormone. The fact that large anterior hypothalamic lesions in the rat (35, 130, 131) prevent the usual goitrogenic response to propylthiouracil feeding and also prevent compensatory hypertrophy in partially thyroidectomized rats suggests that the hypothalamus is involved in the stimulus to increased TSH secretion in response to a lowered concentration of thyroid hormone in the blood. On the other hand, the evidence that administration of exogenous thyroxine still inhibits thyroid activity in the pituitary stalk-sectioned rabbit (47), or in the rabbit with the pituitary gland transplanted to the anterior chamber of the eye (345), suggests that an increased blood level of thyroxine may act directly on the pituitary gland. This latter hypothesis is supported by the findings of von Euler & Holmgren (344) who found that injection of minute doses of thyroxine into the pituitary gland inhibited thyroid function, whereas similar injections into the hypothalamus did not. These curious findings are comparable with those regarding the feed-back mechanism of adrenal steroids.

TARGET GLAND ACTIVITY AND ELECTRICAL STIMULATION OF HYPOTHALAMUS. *Gonadotrophic Secretion and Hypothalamic Stimulation.* The original experiment indicating that electrical stimulation of the nervous system might result in discharge of anterior pituitary hormone was made by Marshall & Verney (225) who showed that diffuse electrical stimuli applied to the head or lumbar spinal cord of rabbits resulted in discharge of gonadotrophic hormone and therefore ovulation and pseudopregnancy in a large proportion of animals. Similar results were later obtained by Harris (147) in rats in which a state of pseudopregnancy was induced by cranial stimulation. In an attempt to delimit the neural structure involved Harris (148) applied localized electrical stimulation to various regions of the hypothalamus and pituitary gland in anesthetized rabbits and found that stimulation of the tuber cinereum, posterior hypothalamus or pituitary gland directly might result in ovulation or the formation of cystic and hemorrhagic follicles. These results were soon confirmed, in the main, by Haterius & Derbyshire (169) who placed the effective hypothalamic site more anteriorly. Some 9 years after these early results Markee *et al.* (218) found that stimulation of the tuber cinereum in the rabbit evoked discharge of luteinizing hormone and ovulation but that direct stimulation of the pituitary gland failed to give this response unless there were signs of spread of the stimulus. Perhaps the most satisfactory technique for such studies is some variation of the remote control method, whereby a coil, leads and electrodes are implanted subcutaneously so that after the animal has recovered from the initial operation and is conscious it may be stimulated by inducing the voltage from an external field coil. With this technique the same site in the nervous system may be stimulated in repeated experiments and the results in any one animal thereby confirmed several times. By its use it was found (151) that stimulation of the tuber cinereum for as short a time as 3 min. might result in a full ovulation response but that similar stimuli applied to the anterior pituitary, pars intermedia or infundibular stem for periods of up to 7½ hr. were without effect in causing gonadotrophic stimulation. Since the pituitary gland thus appears inexcitable to direct electrical stimulation, these results called attention to the possibility that the hypothalamus normally excites anterior pituitary secretion by some humoral mechanism (151, 218).

The above work made use of the ovulation reflex in the rabbit as a quick indicator of discharge of luteinizing hormone. Stimulation of the hypothalamus with observation of changes indicative of secretion of FSH or luteotrophic hormone have rarely been made since the slow nature of the phenomena involved en-

tails technical difficulties. In recent work Donovan & van der Werff ten Bosch (83, 85) found that electrical stimulation of the anterior hypothalamus over periods of 12 weeks failed to induce estrus in female ferrets during the winter. Since lesions in the same sites in anestrous ferrets brought them into heat, the possibility exists that FSH secretion is normally regulated by an inhibitory neural mechanism and from the present data it would seem more reasonable to see whether electrical stimulation of the anterior hypothalamus inhibited, rather than elicited, estrus.

ACTH Secretion and Hypothalamic Stimulation. de Groot & Harris (72) and Hume & Wittenstein (188) first reported that electrical stimulation of the hypothalamus in the conscious animal resulted in a discharge of ACTH as shown by a lymphopenia in the rabbit (72) and an eosinopenia in the dog (188). In both these studies the remote control method of stimulation was used. Later workers have confirmed these results, using the eosinopenic response and implanted electrodes with leads through the skin in the cat (5, 270) and in the monkey (271). The site in the hypothalamus from which such responses are obtained has been given as the posterior tuber cinereum (72, 185, 270, 271), mammillary bodies (72, 270, 271) and more anteriorly in the median eminence (5, 185). Surrounding areas in the hypothalamus did not evoke the response and neither did direct stimulation of the pituitary gland itself (72).

TSH Secretion and Hypothalamic Stimulation. It is claimed (73) that electroshocks applied diffusely to the heads of guinea pigs result in cytological signs of thyroid activation and an increase in TSH in the circulation within 30 min. More localized stimulation of the hypothalamus was performed in rats and rabbits by Colfer (56) who found histological signs of increased activity in the thyroid providing stimulation was applied for at least four 1-hr. periods on each of 2 days. No optimum site for the response was found in the hypothalamus, but control stimulation of the thalamus or corpus callosum was without effect.

More recently (164, 165) electrical stimulation of various areas in the hypothalamus and pituitary gland has been carried out using the remote control method for stimulation in unanesthetized rabbits, and the rate of release of thyroidal I^{131} and the blood concentration of protein-bound I^{131} for assessing thyroid activity (fig. 6). Out of 43 rabbits stimulated, 9 animals showed increased thyroid activity that appeared in every way similar to that following an injection of thyrotrophic hormone. A striking feature is the finding that after adrenalectomy (with cortisone

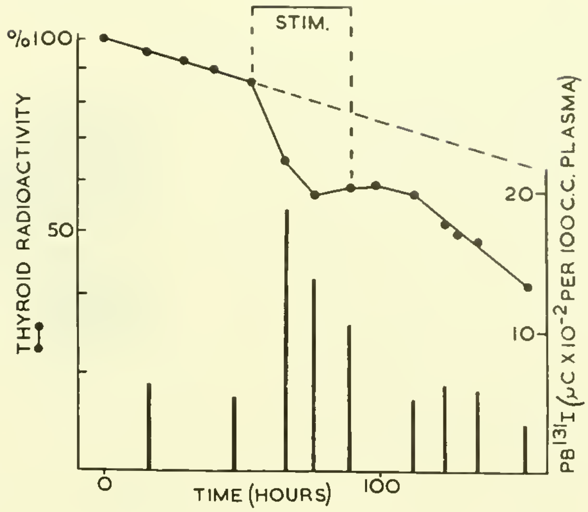

FIG. 6. To show the effect of electrical stimulation of the median eminence on the biological decay of thyroidal radioactivity (I^{131}) and on the blood level of PBI^{131}. Adrenalectomized and ovariectomized rabbit. Previous to adrenalectomy, stimulation had resulted in thyroid inhibition. [From Harris, G. W. & J. W. Woods, unpublished observations.]

maintenance), 13 of 26 of the same animals showed a clear-cut increase of thyroid function on stimulation. Of these 13 animals, 10 had shown no thyroid response before adrenalectomy; in the other 3 animals the response was markedly increased after adrenalectomy. This change in response seems due to the removal of the adrenal cortex since *a*) preliminary denervation of the adrenals did not interfere with the effects of adrenalectomy and *b*) administration of high doses of cortisone to animals with an intact adrenal, in an attempt to block ACTH discharge, often resulted in positive thyroid response to stimulation which had not been seen previously. Since administration of ACTH or compounds B, E or F has been shown to result in diminished thyroid activity in the rabbit and other forms, probably by inhibiting secretion of TSH, and since electrical stimulation of the hypothalamus is known to evoke discharge of ACTH from the anterior pituitary, it seems likely that adrenalectomy is effective since it prevents any sudden rise in the blood concentration of adrenal steroids during the period of stimulation. A noteworthy feature of these results was the fact that hypothalamic stimulation could maintain an increased thyroid activity in the presence of an increased blood concentration of PBI^{131}. This indicates that the influence of the central nervous system can preponderate over the effects of the 'feed-

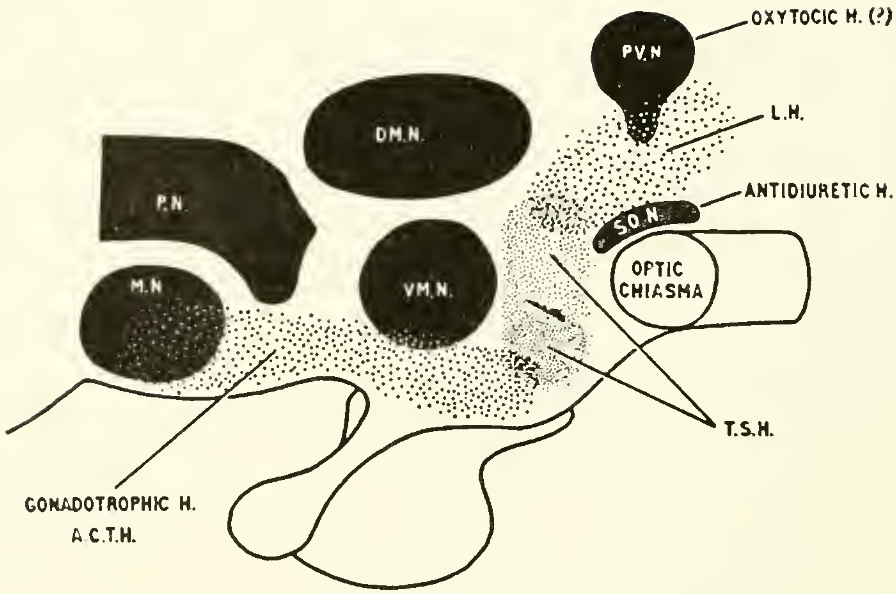

FIG. 7. Diagram of a mid-line sagittal section through the hypothalamus and pituitary gland. Various hypothalamic nuclei (*D.M.N.*, dorsomedial nucleus; *M.N.*, mammillary nuclei; *P.N.*, posterior nucleus; *PV.N.*, paraventricular nucleus; *SO.N.*, supraoptic nucleus; *VM.N.*, ventromedial nucleus) are indicated in *black*. The *stippled areas* indicate the sites where electrical stimulation or lesions have resulted in changes of pituitary secretion. [From Harris (157).]

back' mechanism. The hypothalamic site effective in producing an increased thyroid activity on stimulation is in the region of the supraopticohypophysial tract. This agrees well with the region in which lesions are followed by a diminution in thyroid activity. These results seem to bear a relation to factors which seem of importance in the etiology of Graves' disease [see discussions by Levin & Daughaday (209) and Harris & Woods (165)]. The fact that too prolonged stimulation of the hypothalamus in adrenalectomized rabbits, in which thyroid activation occurs, may result in death of the animal is possibly related to the fact that cortisone administration forms an effective therapy in humans with thyrotoxic crises.

HYPOTHALAMIC LOCALIZATION OF PITUITARY FUNCTION. It is likely that the control of the secretion of the different pituitary hormones is represented by neural mechanisms localized in different regions of the hypothalamus, and that the areas concerned with different hormones could be plotted on a map in a similar way to the representation of the regions of the body in the motor and sensory areas of the cerebral cortex. In the latter case, however, the position is much simplified in that a two-dimensional surface is involved and that the afferent and efferent fibers all approach this surface from one direction. In the case of the three-dimensional hypothalamus, it would seem unlikely, if the above conjecture is in any way true, that future work will result in a simple picture of hypothalamic localization since a multitude of reflex fibers, both excitatory and inhibitory in nature, must pass through the hypothalamus with an eventual convergence in the region of the 'final common path'—the tuber cinereum and pituitary stalk. However, from the meager information available at present, the position may be summarized as in figure 7.

TARGET GLAND ACTIVITY AND EXTRAHYPOTHALAMIC REGIONS OF CENTRAL NERVOUS SYSTEM. Emotional stress is a potent factor in disturbing the normal pattern of endocrine activity. The classic work of Cannon and his colleagues relating adrenal medullary activity with emotional excitement, of Verney and his coworkers in relating similar mental states with discharge of posterior pituitary antidiuretic hormone, and of later workers who found increased secretion of adrenocorticotrophic hormone and decreased release of thyrotrophic and gonadotrophic hormones under these conditions may all be quoted in support of the above statement. The term emotional stress is clearly a very general term and it is likely that certain types of emotional upsets may be more specifically related to certain endocrine disturbances than are others (for example the fear of pregnancy in connection with the sudden onset of amenorrhea in the human female). However in the present context there can be little doubt that parts of the central nervous system, remote from the hypothalamus, may markedly modify endocrine activity. The effect of conditioned stimuli in eliciting or inhibiting hormonal release, such as the well-known discharge of oxytocic hormone that may follow preparation for milking or suckling, may also be mentioned. It is felt that further information

might be obtained in the human by a careful and well-controlled study of the potentiality of hypnotic suggestion to modify endocrine activity, such as a study of the concentration of protein-bound iodine in the blood following the suggestion of a cold external environment.

At the present time data relating different cerebral cortical areas, rhinencephalic structures or other regions of the nervous system to anterior pituitary function are scanty. The general implication in many reports [see the excellent review by Klüver (202)] is that the hypothalamus and hypophysis form a basic unit underlying endocrine activity but that other areas of the central nervous system may exert a regulating influence through projections to the hypothalamus. The term 'basic unit' is used since there is some evidence that animals in which the hypothalamus has been entirely separated from the rest of the central nervous system may show signs of hypothalamoneurohypophysial function (i.e. normal water balance, no polyuria) and of hypothalamoadenohypophysial function (i.e. development of estrus) (15), although such signs of function may be absent after hypothalamic lesions or section of the pituitary stalk. Observation of the effects of lesions in distant parts of the central nervous system on endocrine function were made by Klüver & Bartelmez (203) on a monkey subjected to bilateral removal of both prefrontal lobes and temporal lobes. This animal developed, among other signs, polydipsia, bulimia with progressive adiposity, hyperplasia of the rete ovarii and an extensive endometriosis, results which the authors felt might be attributed to degeneration of fibers to the hypothalamus. Lesions in the region of the amygdaloid nuclei are now well known to result in abnormal sexual behavior, but such a result may be due to factors other than endocrine dysfunction. A more direct relationship between the amygdaloid nuclei and endocrine activity is that reported by Woods (362) who found that lesions in the amygdaloid nuclei of wild rats results in atrophic changes in the adrenal glands. Richter (281) has noticed that similar lesions in the wild rat tend to restore regular activity cycles which are, in all probability, related to the estrous cycles of these animals. Porter (271) has also drawn attention to a possible relationship between the hippocampal region and the secretion of ACTH. He reports that electrical stimulation of the hippocampal area, in particular the uncus, in monkeys inhibited the eosinopenia which normally follows administration of epinephrine or operative trauma. In further experiments the same worker found that electrical stimulation of the orbital surface of the frontal lobe resulted in a marked eosinopenia. Such observations as those just mentioned may safely be taken as the starting point in a wide and new field of research. At the moment the significance of such results is difficult to interpret. In several cases the endocrine effects may be secondary to changes in the 'emotional state' of the animal, rather than due to a direct effect of the region under investigation on the hypothalamus. However, one may be sure that experimental data in this field will be rapidly forthcoming in the future.

ENDOCRINE ACTIVITY AND DEVELOPMENT OF NERVOUS SYSTEM. It has been suggested that, in a general way, the pituitary stalk may be looked upon as the anatomical and functional link between the endocrine system and the external environment. In this case the question may be asked at what stage in the development of the organism does the stalk become functionally active, taking into consideration the fact that exposure to a varying environment occurs only after birth. Detailed discussions of this topic are available (155, 196).

The gonads, thyroid and adrenal cortex appear to be functionally active and secreting hormones before birth. There is also evidence that the activity of the fetal adrenal cortex is to some extent dependent on the secretion of ACTH by the fetal pituitary For example, removal of the pituitary (i.e. decapitation) of the rat or rabbit fetus results in adrenocortical atrophy (195, 348), although decapitation combined with the injection of ACTH in the rat fetus increases the size of the gland above the controls (348). There is also evidence that a feed-back mechanism exists in the fetal pituitary-adrenal cortex system, as in the adult, since Kitchell & Wells (199) found that cortisone prevents compensatory hypertrophy of the adrenal in the fetus. However, the well-known effect of stress in discharging ACTH from the anterior pituitary gland of the adult does not obtain in the newborn. Jailer (191) found in rats that injection of epinephrine does not excite pituitary discharge of ACTH till the 8th day of life and that exposure to cold was ineffective till the 16th day. Somewhat similar results were obtained by Thompson & Blount (327) in newborn mice. Now since the adrenal cortex of the newborn animal is able to respond to injection of ACTH (37, 192, 283, 327), and since Rinfret & Hane (283) have shown the anterior pituitary of 4- to 7-day-old rats contains appreciable amounts of ACTH, the possibility is raised that the lack of sensitivity of the pituitary-adrenal axis of the newborn

animal is due to lack of development of some neural (possibly a hypothalamic) mechanism. As an interesting speculation the pituitary-adrenocortical function of the newborn animal may be compared with that of the adult animal with a cut pituitary stalk.

The data regarding the onset of activity of the gonads are similar to that given for the adrenal cortex. A certain endocrine activity of the ovary and testis is established before birth. Also it is clear that the gonads are capable of responding to gonadotrophic hormone before puberty occurs, and that the anterior pituitary contains and is capable of liberating gonadotrophic hormone before puberty. The evidence indicates that the central nervous system plays an important part in triggering and maintaining the activity of the system at and after puberty. The question has been more fully discussed (156) and more direct data brought forward in support of this view since it has been found that hypothalamic lesions may result in advancement in the date of puberty in the rabbit (119) and rat (84).

Conclusions Regarding Central Control of Adenohypophysis

There can be little doubt that changes in the external environment, acting through the central nervous system, can exert a major regulating influence upon endocrine function. This widespread influence is brought about, in the main, through the intermediation of the hypothalamus and hypophysis. In discussion of the anatomical pathway from the hypothalamus to the hypophysis, attention has been drawn to the absence or scarcity of nerve fibers passing from the former to the latter structure. The only constant anatomical link between the diencephalon and anterior pituitary gland lies in the neural pathways of the hypothalamus to the median eminence of the tuber cinereum and the vascular path, the hypophysial portal vessels, passing from the median eminence to the pars distalis. There is strong evidence that this neurovascular path forms the route by which the hypothalamus influences anterior pituitary activity. How this control is mediated is unknown. The most likely view, based on general data regarding humoral transmission of nerve impulses and current views on the mode of formation of posterior pituitary hormones, is that a humoral substance or substances are liberated by nerve endings into the primary plexus of the portal vessels and transmitted by these vessels to effect changes in activity in anterior pituitary cells. Indirect evidence in support of this view is available but direct evidence, according to various criteria laid down for the study of this problem, is lacking.

In order to estimate the degree of dependence of the endocrine system on the central nervous system, it is necessary to know the intrinsic autonomous activity of the anterior pituitary gland and its target organs when separated from the central nervous system (by pituitary stalk section or pituitary transplantation). Much data are available on this point. It seems that the endocrine activity of the gonads almost entirely ceases, although thyroid and adrenocortical activity continues at a reduced level under these conditions. Thyroid function is still modified by an increase in the blood concentration of thyroid hormone (indicating that such a change exerts an effect directly on anterior pituitary cells), and the activity of the thyroid and adrenal cortex seems to be still influenced by 'systemic' stresses (in Fortier's sense of stresses involving tissue trauma or metabolic disturbance).

The feed-back mechanism, by which the blood concentration of target organ hormones affects the liberation of anterior pituitary hormones, appears to perform a stabilizing function by which the pituitary-target organ system maintains endocrine activity at a constant level under conditions of a constant environment. Although data are accumulating, it cannot yet be stated clearly what part the hypothalamus plays in this feed-back mechanism.

The responsibilities of the central nervous system, with regard to endocrine activity, may be discussed under three main headings. First, it must initiate in the newborn animal or in the prepubertal animal the adult pattern of endocrine function and maintain this level of function. The gonads are the target organs most wholly dependent on some neural stimulus to the adenohypophysis. Not only the onset of gonadal activity at puberty and the maintenance of this activity in the adult above the prepubertal level, but the different patterns of gonadotrophin secretion seen in the male and female animal appear dependent on the nervous system. The secretion of TSH and ACTH at a normal level is also dependent on the nervous system, although apparently not to the same degree as is secretion of gonadotrophic hormone. Recent data indicate that the hypothalamus may mediate both excitatory and inhibitory influence over the secretion of anterior pituitary hormones. Second, the nervous system is responsible for mediating the effects of stimuli arising from a changing external environment. Changes in the external environment which are sufficiently intense to result in tissue trauma or metabolic disturbances are possibly capable of affecting anterior

pituitary secretion through the general systemic circulation, but the majority of environmental stimuli (arising from such factors as changing conditions of light, temperature, sound, presence or absence of a mate and so on) exert their effects through the nervous system. And third, it appears likely that the hypothalamus acts as an integrating mechanism whereby the effects of afferent nervous impulses derived from sensory stimuli, changes in the emotional or psychological state and perhaps from changes in the concentration of target-organ hormones in the blood are correlated and coordinated and the resultant 'stimulus' to the adenohypophysis transmitted down the 'final common path' of the pituitary stalk. The hypothalamus seems to be in a key position for integrating not only patterns of endocrine activity but also patterns of emotional behavior, and it is possible that these two functions are closely linked (cf. the effect of estrogens on patterns of sexual behavior and discharge of gonadotrophic hormone, or the effect of emotional excitement on the discharge of anterior pituitary hormones and adrenal medullary hormones) at this forebrain level.

NEUROHYPOPHYSIS

Recent and major advances in the field of central control of the neurohypophysis come from work on neurosecretory mechanisms, and from studies on blood osmotic pressure in relation to posterior pituitary activity and on nervous reflex release of oxytocic hormone in relationship to lactation. The question of neurosecretion is dealt with in Chapter XL by Ortmann in this *Handbook* and will not receive direct attention here. The remainder of this chapter will be devoted to an account of the anatomy of the hypothalamoneurohypophysial system and of the changes in the internal and external environment which reflexly modify the rate of secretion of posterior pituitary hormone or hormones by acting through this system.

Anatomy of Hypothalamoneurohypophysial System

According to the terminology of Rioch *et al.* (284), which is accepted as the standard nomenclature for the hypophysis and its various subdivisions, the neurohypophysis consists of three parts: the infundibular process (lobus nervosus or neural lobe), the infundibular stem and the median eminence of the tuber cinereum. There are many grounds for believing that the neural lobe, the infundibular stem and the expanded upper end of the stalk or median eminence are composed of tissue of a uniform type and different from that of the hypothalamus proper. Evidence for vital staining (361), vascular supply (126, 358, 360), embryology (330) and cytology (120, 346) may be cited in support of this view. There is present then a 'gland' which, from the viewpoint of the naked eye, consists of the neural lobe in the sella turcica, the neural tissue of the pituitary stalk and the expanded upper end of the stalk (median eminence). All this tissue is innervated by the supraopticohypophysial tract, originating in the paraventricular and supraoptic nuclei in the hypothalamus. According to the neurosecretory theory, the hormones of the posterior pituitary gland are formed in these two nuclear groups, transported down the axons of the tract and stored, or liberated into the blood as required, in the three parts of the neurohypophysis. There can be no doubt that the rate of hormonal liberation is controlled by nerve impulses in the supraopticohypophysial tract, the fibers of which then may possess the dual function of a transport system and a secretomotor innervation. If the above views are correct, the question may be asked as to why signs of glandular deficiency occur (diabetes insipidus, failure of the milk-ejection reflex, as described below) when the supraopticohypophysial tract is sectioned between the levels of the nuclei or origin of the tract and the neurohypophysis (*A* in fig. 8). It might be argued that if the hormones are formed in the cells of the paraventricular and supraoptic nuclei, liberation could occur directly from these cells into the surrounding capillaries, especially since these two nuclei are among the most highly vascularized in the brain. Two possible reasons suggest themselves. First, section of the supraopticohypophysial tract is followed by retrograde degeneration and loss of many cells in the supraoptic and paraventricular nuclei (see 156; 275, p. 193). Possibly too few secreting cells are left to prevent hormonal deficiency. And second, the blood vessels of the hypothalamus proper may be impermeable to the polypeptide (or larger) molecules comprising the hormones. The permeability of the hypophysial vessels seems to be very different from that of the hypothalamus (361) and it is possible that, even if sufficient hormone is formed in hypothalamic neurones, it would be unable to pass into the blood stream unless transport to the neurohypophysis is possible.

The anatomy of the nerve supply to the neurohypophysis was first described by Ramón y Cajal

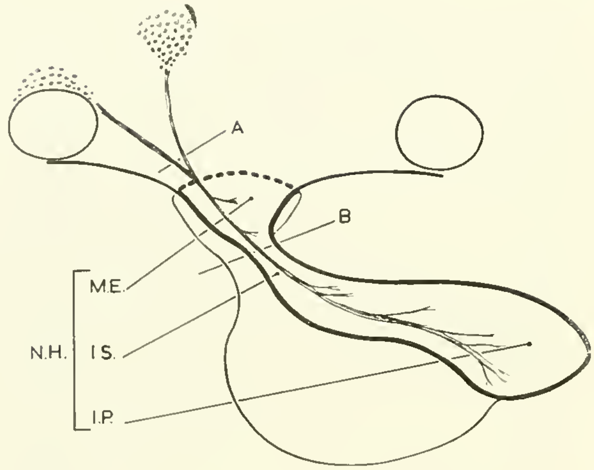

FIG. 8. To illustrate the main innervation of the neurohypophysis, derived from the supraoptic and paraventricular nuclei of the hypothalamus. The neurohypophysis (*N.H.*) consists of the median eminence (*M.E.*), the infundibular stem (*I.S.*) and the infundibular process (*I.P.*). Section of the supraopticohypophysial tract at *B* leaves a part of the gland still innervated and may not result in signs of deficiency, whereas section of the tract at *A* causes atrophy and loss of function of the whole gland.

(272). A detailed description and a comprehensive list of early references (up to 1938) dealing with this subject may be found in the monograph of Fisher *et al.* (100). The hypothalamohypophysial tract, which includes all nerve fibers running from the hypothalamus into the neurohypophysis, may be subdivided into the important supraopticohypophysial tract running in the anterior or ventral wall of the stalk, and a tract about which very little is known, the tuberohypophysial tract, running in the posterior or dorsal wall of the stalk. The supraopticohypophysial tract can be seen in good microscopic preparations to take origin from the cells of the paraventricular and supraoptic nuclei, and to collect in a definite bundle of fibers [about 10,000 fibers in the rat, 60,000 in the dog and 100,000 in man, according to Rasmussen (275)] in the median eminence, most of which pass through the infundibular stem to the neural lobe. The histological termination of these fibers, in all three parts of the neurohypophysis, is obscure although it appears significant that perivascular endings have been described as common, especially in certain forms (where they are easy to visualize) such as the opossum (34, 125).

Section of the supraopticohypophysial tract in the region of the infundibular stem (*B* in fig. 8) has been shown (100, 215) to result in atrophy and hypercellularity of the neural lobe and a loss of nerve fibers and of pressor, antidiuretic and oxytocic substances in the denervated gland. The upper end of the stalk and median eminence, however, show an increase in volume (24, 27, 50, 323) and an increase in Gomori stainable material (27, 323). Further an increase in extractable antidiuretic (213, 293) and oxytocic substances (245) in the hypothalamus has been reported. These data show that any part of the neurohypophysis separated from its nerve supply undergoes atrophy and loss of function. If the upper end of the stalk or median eminence is left innervated, some process of reorganization, and return of function, may occur. However, there is little evidence of any residual neurohypophysial activity if the supraopticohypophysial tract is interrupted above the level of the median eminence (*A* in fig. 8).

Nervous Reflex Modifications of Neurohypophysial Activity

In the following discussion the phrase 'neurohypophysial activity' will be taken to mean the rate of release of hormones from the neurohypophysis into the blood stream. The hypothalamus may be said to be related to neurohypophysial activity in the following ways.

a) The activity of the gland seems entirely dependent on its connections with the hypothalamus.

b) Changes in the 'milieu intérieur,' especially changes in the osmotic pressure of the blood, may affect the activity of the gland profoundly through the intermediation of the hypothalamus.

c) Changes in the external environment, particularly those giving rise to stimulation of the reproductive organs (nipples and external genitalia) and those calculated to give rise to emotional excitement, also affect the activity of the gland through nervous reflexes acting via the hypothalamus.

REFLEX CONTROL OF ANTIDIURETIC HORMONE (ADH) SECRETION. The relationship between hypothalamic lesions and diabetes insipidus was first clarified by the studies of Fisher *et al.* (100). These workers used the Horsley-Clark sterotaxic apparatus to make small localized electrolytic lesions in the hypothalamus of the cat and found that bilateral lesions in the course of the supraopticohypophysial tract, but in no other hypothalamic sites, resulted in a condition similar to that of clinical diabetes insipidus. They described the typical phases of onset of the diabetes and gave a detailed description of the histological findings in the hypothalamus and pituitary gland of their animals.

These results were confirmed in the monkey, both by placing electrolytic lesions, and later by Magoun *et al.* (215) by pituitary stalk section. The important contribution of this group was the demonstration that the hypothalamus-neurohypophysis functions as a unit and that it is the supraopticohypophysial tract which is the important connecting link between the two structures. It is on the basis of these studies that the concept that neurohypophysial activity is completely dependent on its innervation may be considered established.

The obvious experimental corollary to the work of Ranson and his group that electrical stimulation of the supraopticohypophysial tract elicits increased release of ADH—has been most clearly established by using unanesthetized animals (149). With the remote control method of stimulation it has been possible to demonstrate that a release of ADH, with a resultant inhibition of water diuresis, follows electrical stimulation of the supraopticohypophysial tract in the hypothalamus, median eminence, infundibular stem or infundibular process. The duration of the antidiuretic response could be correlated with the intensity of the stimulus, and the responses in any one animal to a given stimulus remained remarkably constant over periods of weeks or months. The fact that the supraopticohypophysial tract may be stimulated electrically, with typical 'secretomotor' responses, makes it seem very likely that these fibers conduct nerve impulses and regulate neurohypophysial activity as does the secretomotor innervation of other glands.

The idea that neurohypophysial activity is affected by the composition of the blood, especially by changes in the osmotic pressure of the blood, was put forward by Klisiecki *et al.* (200, 201) to explain the mechanism of a water diuresis. They suggested that ingestion and absorption of water results in a decreased osmotic pressure of the blood and consequent inhibition of the secretion of antidiuretic hormone with a resultant diuresis which begins after the hormone already in the blood stream has been removed or inactivated. The effect of increasing the osmotic pressure of carotid blood on neurohypophysial activity has been investigated in detail by Verney and the results reviewed (338, 339). Verney found that an injection of isotonic solution of sodium chloride into the carotid artery, or of hypertonic solutions (up to 20 cc of 0.343 M NaCl in 20 sec.) intravenously did not inhibit a water diuresis. However, injection of similar hypertonic solutions into the carotid artery resulted in marked inhibition in the course of a water diuresis, a response that very closely simulated that following intravenous injection of posterior pituitary extract. The pituitary origin of the response was established by the observation that surgical removal of the neural lobe of the pituitary reduced the response to about 10 per cent of that obtained previously. More prolonged infusions of sodium solution were then studied to obtain information regarding the smaller and longer-lasting changes in osmotic pressure of the blood likely to occur in the normal animal. In this connection results of experiments involving 10- and 40-min. infusions of hypertonic saline showed that a rise of only 1 per cent in the osmotic pressure of aortic blood would probably reduce a water diuresis to only 10 per cent of the maximum rate of urine output, a response which would correspond to a release of about 1 μU per sec. of antidiuretic substance. The site of the osmoreceptor mechanism is not clearly established. There are data indicating that it is located in the territory of supply of the internal carotid artery and that it lies in the diencephalon but not in the neurohypophysis (194). The most probable site is the supraoptic nuclei, a site suggested by the extremely vascular nature of these cell groups and by the specialized intracellular vesicles found there (193).

Emotional stress seems a potent factor in eliciting secretion of ADH. Rydin & Verney (289) investigated the mechanism whereby forced running in dogs evoked an antidiuretic response. They found that if animals were repeatedly exercised the inhibitory response on urine flow progressively diminished to final extinction, and for this and other reasons suggested that it was not the exercise per se, but the emotional accompaniment, that was the effective stimulus. From experiments involving kidney and adrenal denervation it was concluded that the renal response to emotional stress is due to some agent humorally conducted to the kidney, and that the agent was not epinephrine but possibly antidiuretic hormone. This view was put beyond doubt by the findings of O'Connor & Verney (251) and O'Connor (250) that removal of the posterior lobe of the pituitary or section of the supraopticohypophysial tract greatly reduced the antidiuretic response to emotional stimuli. It seems that stimuli which are calculated to give rise to emotional excitement activate nervous pathways to the supraoptic nuclei which in turn evoke the release of ADH from the neurohypophysis. The anatomy of any afferent pathways to the supraoptic nuclei is unknown. The studies of Pickford and others, however, indicate that at least some of these fibers are cholinergic in nature (87, 98, 261–263).

REFLEX ACTIVATION OF OXYTOCIC HORMONE SECRETION. The effects of oxytocic secretion may be observed on the lactating breast and on the uterus. Such secretion appears to be evoked by direct stimulation of the reproductive organs (nipple, external genitalia or uterine cervix) and also by conditioned reflexes. It has been established that nervous reflex release of oxytocic hormone plays a necessary role in milk ejection from the lactating breast, and it appears probable that a similar mechanism underlies the processes of parturition and of sperm transport up the female reproductive tract.

Oxytocic hormone and milk-ejection reflex. It has long been known that the transfer of milk from the lactating breast to the suckling young involves an active expulsion of milk from the mammary gland. Gaines (114) showed many years ago that suckling pups cannot obtain milk from an anesthetized bitch. Petersen and his co-workers (89, 258, 259) first brought forward evidence that secretion of oxytocic hormone forms an essential part of the physiological mechanism underlying milk ejection. They found that cutting the motor nerves to one half of the udder of the cow had no effect on the amount of milk obtained from that half of the udder, and that milk ejection could be stimulated in the isolated perfused udder by addition of oxytocin to the perfusing blood or by the addition of blood withdrawn from the jugular vein of a cow recently subjected to a milking stimulus. A few years after these observations Richardson (279) demonstrated clearly the myoepithelial cells which form basketlike networks around individual alveoli and around the ducts of the breast and which in all probability represent the contractile tissue of the organ.

More direct evidence for the involvement of the supraopticohypophysial tract and the neurohypophysis in the mechanism of milk ejection came from the independent researches of Cross & Harris (63) on rabbits and Andersson (7, 8) on sheep and goats. Cross & Harris found that electrical stimulation of the supraopticohypophysial tract in the hypothalamus, infundibular stem or infundibular process in the lactating rabbit evoked ejection of milk from a cannulated teat duct. The time course of this response had the character of one humorally mediated and could be duplicated very closely by intravenous injection of posterior pituitary extract. In further experiments it was found that electrolytic lesions placed in the supraopticohypophysial tract markedly reduced the amount of milk obtained by a suckling litter, unless posterior pituitary extract was injected into the doe immediately before suckling. Andersson observed a flow of milk from the teats of unanesthetized sheep and goats following stimulation of the supraoptic nuclei by the Hess technique. Denervation of the udder or of the whole sacral region of the goat did not affect the result, although a similar response was obtained following the injection of blood of another stimulated animal. These results have since been extended by Cross (60, 62) who has investigated in more detail the effects of hypothalamic stimulation, by Cross & van Dyke (64) who found purified oxytocic hormone to be about six times as effective in eliciting milk ejection as purified antidiuretic hormone, by Harris & Jacobsohn (161) who studied lactation after pituitary transplantation in rats, and by Benson & Cowie (24) who investigated the milk-ejection reflex after removal of the infundibular process. Very little is known regarding the reflex nervous pathways to the supraoptic (and paraventricular) nuclei which underlie the milk-ejection reflex. There can be no doubt that conditioned reflexes play a large part in exciting the reflex in the normal animal, but the sensory path from the nipples to the hypothalamus might profitably be investigated in the anesthetized animal.

Oxytocic hormone and parturition. The essential nature of the hypothalamoneurohypophysial system for normal parturition has not yet been demonstrated. It has been observed (79, 101) that the majority of cats and guinea pigs in which hypothalamic lesions have induced a state of diabetes insipidus are either unable to deliver their young or deliver them after a prolonged and difficult labor. However, a few animals [slightly less than one third (79)] do appear to undergo normal parturition in the presence of a denervated neurohypophysis. The potentiality of the neurohypophysis to evoke strong uterine contractions has been made clear by studies in which the supraopticohypophysial tract has been stimulated electrically. Haterius & Ferguson (170) and Ferguson (99) found that electrical stimulation of the pituitary stalk of *post partum* rabbits resulted in an increased frequency, and sometimes increased amplitude, of uterine contractions. Harris (149) studied the uterine response of estrous or estrogenized rabbits to remote-control stimulation of different areas in the hypothalamus or pituitary. Stimulation of the region of the supraopticohypophysial tract, but not other areas, was found to result in a well-marked uterine response which had the characters of one humorally mediated and which could be closely duplicated by injection of

posterior pituitary extract (in doses of up to 200 to 500 mU of the oxytocic fraction).

The clearest evidence that the neurohypophysis is normally concerned in labor comes from the experiments of Ferguson (99). In a study on rabbits 8 to 48 hr. after parturition, he found that dilatation of the body or cervix of the uterus or vagina stimulates a nervous reflex release of oxytocic hormone and an increase in the contractions of the body of the uterus. This response was abolished by section of the spinal cord or by hypophysectomy. On this and other evidence Ferguson suggests that the mechanism of parturition involves reflex stimulation of oxytocic secretion, probably in amounts varying with the part of the reproductive canal undergoing dilatation. That oxytocin is secreted during parturition is indicated by the observation (142) of a woman still lactating from a previous pregnancy who came into labor. The mammary expulsion of milk was observed to coincide with the labor pains and was duplicated by the injection of pituitrin at the end of the second stage of labor.

In summary, it is very probable that reflex excitation of the neurohypophysis is involved in normal parturition, but it is possible that other factors, such as the motor innervation of the uterus and contractions of the abdominal wall, may compensate for loss of the gland in some cases.

Oxytocic hormone and sperm transport. There is good evidence that in many animals, including the rat, guinea pig, dog, rabbit, sheep and cow, sperm (whether alive or dead) reach the upper end of the uterus within a few minutes from insemination, that is with a speed that cannot be accounted for in terms of sperm motility. Ever since the observations of Heape (172) in 1898, it has been suspected that increased uterine contractions after coitus might facilitate the transport of seminal fluid and the fact that mechanical stimulation of the vulva was found to result in such increased motility of the uterus (172, 204) supported this view. Following the observation that electrical stimulation of the supraopticohypophysial tract resulted in a marked uterine response in the estrous rabbit it was suggested (149) that coitus may excite a nervous reflex release of oxytocin with a resultant increase in motility of the uterus. Millar (243) measured the intrauterine pressure in the mare during mating and found that a considerable negative pressure developed and that up to 80 ml of fluid might thereby be sucked into the uterus. Van Demark and his colleagues have studied the problem in cows and found an increased uterine motility following mechanical stimulation of the vulva and cervix (334), an increase in uterine tone and contractions when the bull is brought into sight of the cow and a further increase during mating (335), and an increase in intramammary pressure (perhaps a more certain indication of oxytocin release than increased uterine motility) after manipulation of the vulva and cervix uteri (171). In this latter connection it is of interest that coitus excites milk ejection in lactating women (49, 163, 264).

At the moment the data are suggestive that nervous reflex release of oxytocic hormone plays a role in sperm transport. However, from the fact that conception may occur in the presence of diabetes insipidus it would appear that the neurohypophysis plays only a supporting, rather than an essential, role in this respect, a conclusion similar to that regarding its function during parturition.

Adrenal Medullary Hormones and Nervous Reflex Activation of Neurohypophysis

It is well known that the hypothalamus is intimately concerned not only with the release of posterior pituitary hormone or hormones but with the release of the hormones of the adrenal medulla. In recent years it was found by O'Connor & Verney (252) that an increased blood concentration of epinephrine may block the nervous reflex release of antidiuretic hormone. Somewhat similar results were obtained by Cross (60, 61) who studied the reflex discharge of oxytocic hormone from the neurohypophysis. Cross found that administration of exogenous epinephrine, or an increase in the blood concentration of adrenal medullary hormones produced by stimulation of the more lateral region of the hypothalamus, might block a reflexly excited release of oxytocic hormone and might also block the effect of injected oxytocic hormone in producing milk ejection. The fact that emotional stress (forcible restraint) frequently resulted in inhibition of the milk-ejection reflex to suckling but did not affect the response to injection of oxytocic hormone led to the conclusion (61), ". . . the main factor in emotional disturbance of the milk-ejection reflex is a partial or complete inhibition of oxytocic release from the posterior pituitary gland."

These studies demonstrate again the close relationship that appears to exist between different emotional states and endocrine activity, and indicate a further integrative function of the hypothalamus in this respect.

Further advances in knowledge of the central

nervous control of the pituitary gland appear largely attendant on development of techniques, and especially of those associated with the collection of pituitary venous blood in the conscious animal and with the assay of this blood for posterior and anterior pituitary hormonal activities.

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Neurosecretion[1]

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CHAPTER CONTENTS

HISTORICAL INTRODUCTION AND NOMENCLATURE

THE FINDING of 'gland-like' cells in the spinal cord of sharks by Dahlgren (75) and Speidel (305) constituted the first observations on secretory activity in nerve cells. The investigators Collin, Scharrer, Hanström, Roussy and Mosinger are associated with a period of research during which a large number of significant observations on the hypothalamus and neurosecretion were accumlated. To Ernst Scharrer belongs the credit for having positively demonstrated the secretory activity of special groups of neurons. In collaboration with Berta Scharrer, he led the research on neurosecretion to most fruitful results. The work at this time, however, was somewhat restricted by the poor and nonspecific stain techniques available. The introduction of the chromhematoxylin stain technique of Gomori represented a key advance and permitted Bargmann (29) to lay the true foundations for this field of investigation. Because the work on neurosecretion is at most 50 years old, it is not surprising that its terms are not yet strictly formulated and are not being uniformly used by the workers involved. Scharrer's original 'hypothalamus gland' and 'neurocrine organs' (279, 280) have only historical significance today.

The term *neurocrinie* (72) indicates the reception of secretory material by nervous tissue. Therefore, it is impossible to use it synonymously with neurosecretion. Barry (39) has employed the term *neurocrinie* to imply the concept of delivery of neurosecretory material to nervous tissue, using for the region of transition the term *synapse neurosecretoire*.

The term *neuricrinie* (268) has been used especially by the workers of the French school as synonymous with neurosecretion. Recently Barry (39) has proposed to include in this term not only neurosecretion but also the secretory activity of neuroglial structures, such as the subfornical and subcommissural organs, the supraoptic crest and possible pineal cells, and the production of neurohormones (208).

Basic to the concept of 'neurosecretion' is the presence of true neurons with axons and dendrites, Nissl substance and neurofibrillae. These cells also exhibit morphologically demonstrable evidence of secretory

[1] English version prepared by K. M. Knigge, Department of Anatomy, University of California, Los Angeles, from the original German. The manuscript was completed February 5, 1956.

activity. Knowles (183) defines neurosecretory fibers as those which end blindly, which have special synapses and which do not excite other neurons or innervate organs in the common sense of the term. It is clear that this definition may already be too restricted in the light of present investigations (40, 194, 253). It has not been determined with certainty whether neurons active in the transport of neurosecretory material are able also to stimulate other nerve cells. The presence of neurofibrillae in such cells is questioned seriously, largely because of technical difficulties in their demonstration (130). However, it is a fact that in vertebrates as well as in invertebrates these neurons are capable of transmitting electrical impulses (49, 245). The term *encephalohydrocrinie* has been coined by Roussy & Mosinger (267) to indicate the delivery of neurosecretory material into the ventricles, a concept of some possible significance which has received little attention outside of the French school of workers

NEUROSECRETORY CELLS AS SPECIALIZED NEURONS

Secretory activity of neurons represents a further specialization of these cells. Like other neurons, cells active in neurosecretion exhibit all the usual morphological evidence of intensive protein synthesis (Caspersson, Hyden) such as enlargement of nucleoli, enlargement and excentric position of nuclei, evidence of nuclear secretion, reconstruction of plasma ribonucleic acids, accumulation of phosphatase enzymes and alteration in amount and distribution of Nissl material as in the axon reaction (56). The streaming of cytoplasm from the region of the perikaryon to the periphery of the nerve cell (335) indicates not only a continuous protein synthesis, but also reflects the movement of material along the axon, as has been observed in living nerve fibers (126, 167). This phenomenon has been demonstrated also with the aid of radioactive materials in both *in vivo* and *in vitro* nerve preparations (66). The observation that living nerve fibers can incorporate and move fluid droplets (126) should be an indication that the finding of vacuoles in ganglion cells is not necessarily an indication of neurosecretion (326). The ontogenetic maturation of the neurosecretory system (263) lends itself easily to correlation with similar development and change in the enzyme systems of nervous tissue observed by earlier investigators (334). Finally, there are signs of a phylogenetic specialization of neurosecretory elements (152, 236, 264).

NEUROSECRETION IN VERTEBRATES

Hypothalamic-Pituitary System Demonstrable with Chromhematoxylin

The most thoroughly investigated field in neurosecretion is that part of the hypothalamic-pituitary system demonstrable through staining with chromhematoxylin or paraldehyde fuchsin.

MORPHOLOGY. In lower forms, the nuclei concerned in this part of the hypothalamic-pituitary system belong to the preoptic nucleus which differentiates into two parts and in reptiles, birds and mammals becomes the supraoptic and paraventricular nuclei. The special position of these nuclei (fig. 1*A*, *B*) is indicated in the case of the preoptic nucleus by the relationship of its dorsorostral part to the third ventricle and its caudoventral part to the ventral surface of the brain. Similarly, in higher forms the paraventricular nucleus lies close to the third ventricle and the supraoptic nucleus can be seen on the ventral surface.

In mammals the neurons constituting these groups may occasionally be disseminated in the form of accessory nuclei (136, 192, 237). Characteristic cells of these nuclear groups may be found distributed also along the pathway of their axons as far as the posterior lobe (29, 144, 196). The axons of cells in the paraventricular nucleus may associate closely with those of the supraoptic nucleus or pursue a separate pathway to the posterior lobe (192). In the dog, the total number of neurons is approximately 90,000. The processes of these neurons end in large measure in the posterior lobe (*neurosecretorische Bahn*) (29, 241). They constitute accordingly the supraopticohypophyseal tract of Greving (137, 138) which, with some species variation, contains both myelinated and nonmyelinated fibers. In lower forms, dendrites of these cells may reach the ventricular wall (152, 214, 236, 266, 317). In all vertebrates, axons of such fibers end partially in the hypothalamus, in the region of the median eminence and in the pituitary stalk as well as in the ependyma of the infundibular part of the ventricle (fig. 1*B*). In earlier work, the common characteristics used to identify these nuclei were the limitation of the Nissl material to the periphery of the cell (variable according to species), the very rich capillary bed and the presence of colloid in the neuron cell body and processes. Currently, greater emphasis is placed upon the cytoplasmic granules and droplets made visible by a number of stain techniques (131) but which are demonstrated to have special characteristics by the

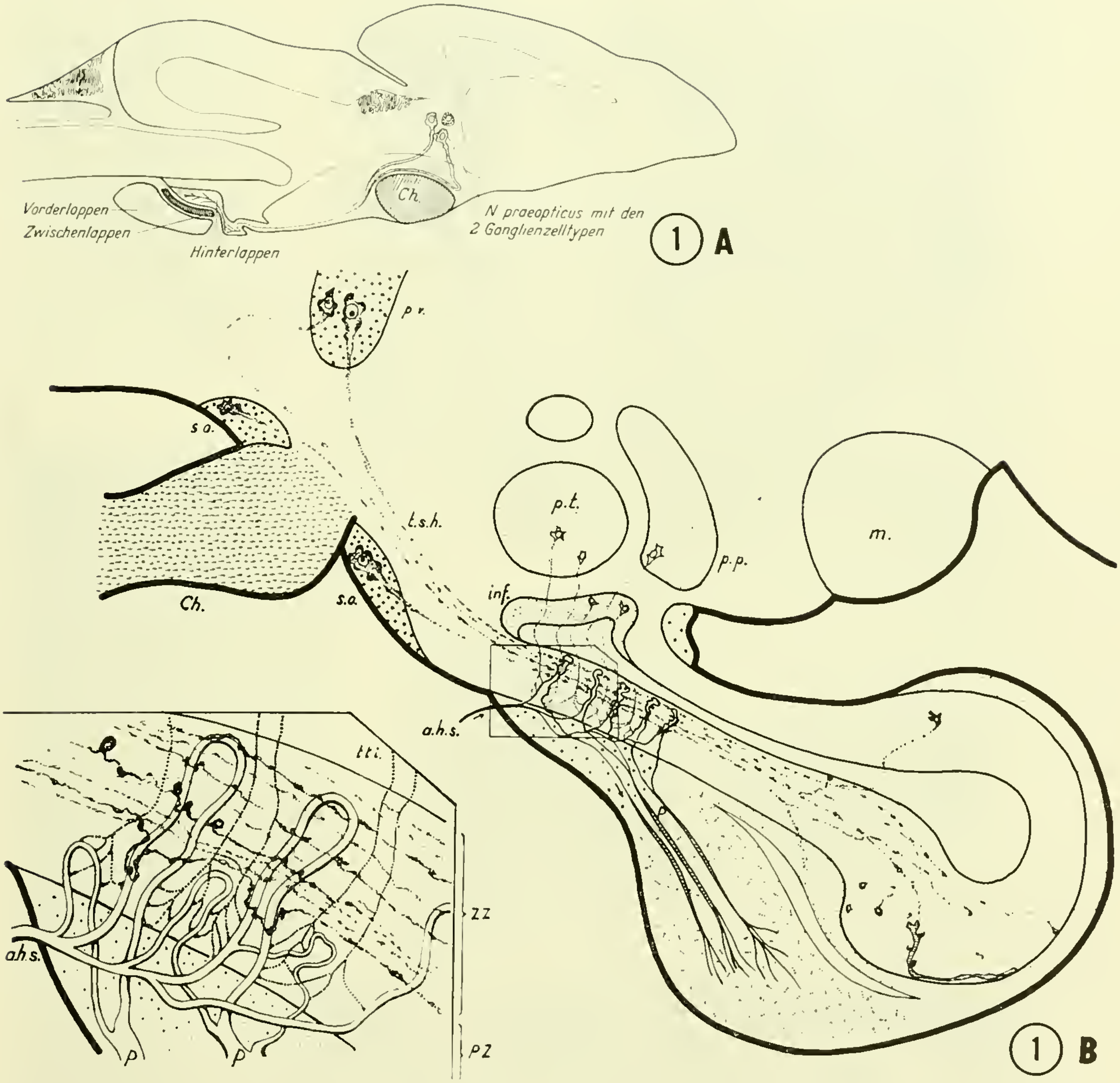


FIG. 1. *A*. Schematic diagram of the preoptic-hypophyseal tract in Anura. [From Hild (164).] *B*. Schematic diagram of the neurosecretory elements of the hypothalamic-pituitary system in mammals (dog and cat), including the supraoptic (*s.o.*)-paraventricular (*p.v.*) tract to the intermediate and posterior lobe and the tuberoinfundibular tract (*t.t.i.*). Of particular interest is the relationship of these fibers to the roots of the portal vessels in the median eminence. Chromhematoxylin-stained fibers from the anterior hypothalamus are situated in the more ventral part of the stalk (central zone, *ZZ*) and come into relationship with the 'special vessels' (232). Axons of the tuberoinfundibular tract, not stained with chromhematoxylin, are collected near the peripheral zone (*PZ*) and pass nearer the base of the special vessels. The enlargement (*insert*) indicates these relationships: *p.t.*, nucleus principalis tuberis; *inf.*, nucleus periventricularis infundibularis; *p.p.*, area periventricularis posterior; *ch.*, optic chiasma; *t.s.h.*, supraopticohypophyseal tract; *m.*, mammallary body; *p.*, portal vessels; *a.h.s.*, branches of the superior hypophyseal artery. [Modified from Engelhardt (100) and Bargmann (29).]

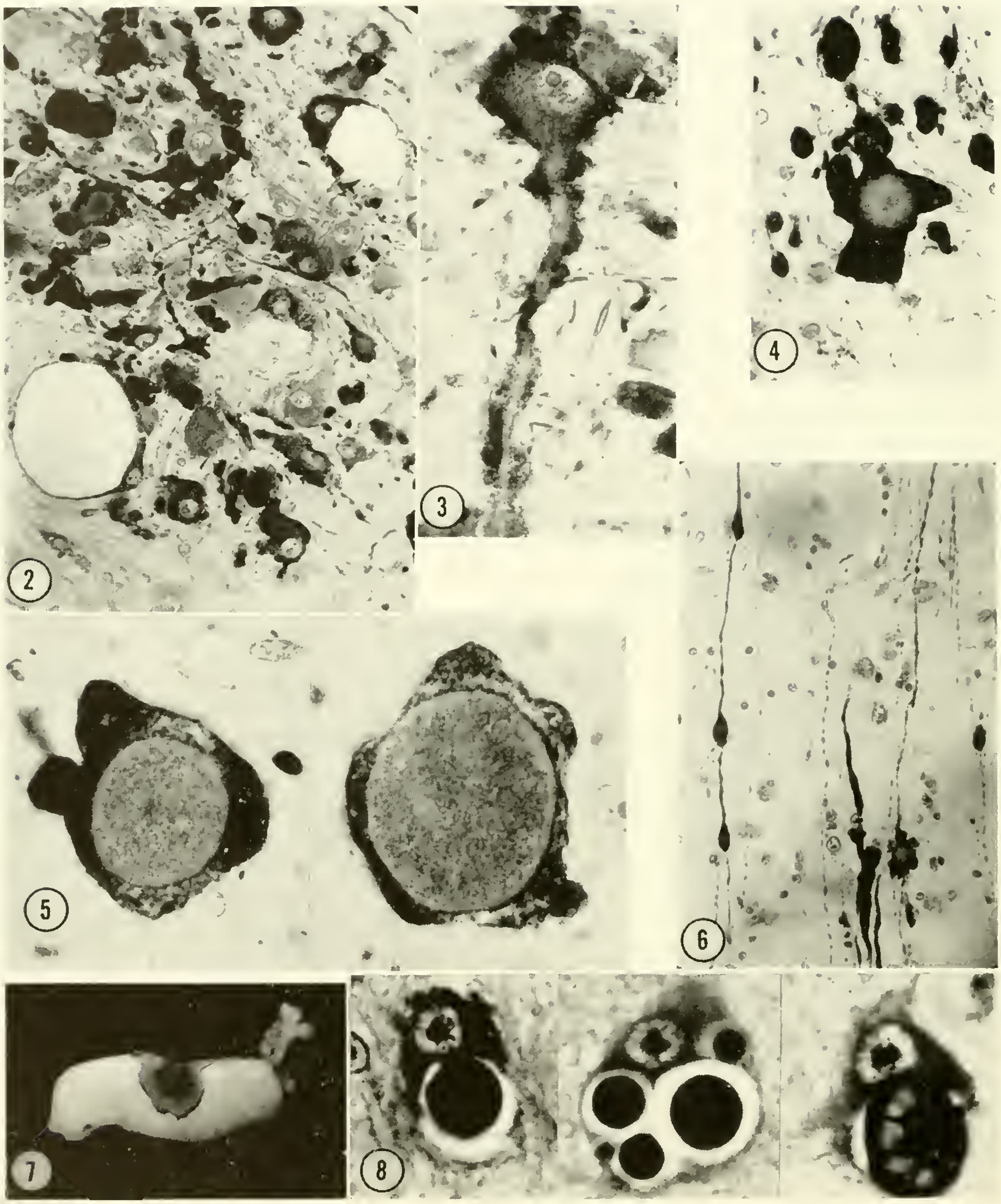


FIG. 2. Ventrocaudal part of the supraoptic nucleus of the dog, showing neuron cell bodies and processes with varying amounts of neurosecretory material. Two large vesiculated neurons (vesicles of Verney) contain a large amount of neurosecretory material and normal nuclear structures. Chromhematoxylin-phloxin stain. × 250.

FIG. 3. Neuron from the supraoptic nucleus of the dog, showing clearly the peripheral distribution of the neurosecretory material in the axon. Chromhematoxylin-phloxin. × 625.

FIG. 4. Herring body in the central portion of the posterior lobe with lobular accumulations of neurosecretory material around the periphery and a clear central area. Chromhematoxylin-phloxin. × 490.

FIG. 5. A large Herring body (90 μ) from the median eminence of *Callithrix* (*Hapale*) *penicillata* showing a clear central area. Chromhematoxylin-phloxin. [From Hanström (151).]

FIG. 6. Neurosecretory fibers of the dog, originating in the paraventricular nucleus (*above*), reach the supraoptic nucleus

four following methods: *a)* chromhematoxylin-phloxin stain according to Gomori (127) introduced first by Bargmann (29) for the demonstration of neurosecretory material, the counterstaining with azophloxin here being of no importance (fig. 2); *b)* the paraldehyde-fuchsin stain according to Halmi (145), standardized and considerably improved by Gabe (109, fig. 10); *c)* a series of histochemical methods for the demonstration of sulfhydryl groups (4, 5, 35); and *d)* the technique of phosphomolybdic acid-congo red staining after formalin fixation (300).

A definite oxidation step is an essential prerequisite for the success of the staining methods *a* to *c* (292), while the congo red method is intensified through a reduction in thioglycolic acid. Furthermore, the staining is dependent upon the interval of time between death and fixation of the tissue (171) as well as the use of definite fixing solutions (Bouin, Helly and Susa fixatives are recommended while alcoholic solutions are contraindicated). With all four methods there is demonstrated a granular intracellular secretory material which corresponds in amount and position to material observed in unfixed preparations examined with phase microscopy and darkfield (245, 288). Within the cell body the neurosecretory material is centrally located in the region about the nucleus (164, 242, 245, 317), while in the axon and its terminations it is always situated superficially. The perikaryon as well as the axon can exhibit irregular bulbous enlargements on their surfaces, while axons always show a thread-like central portion containing much neuroplasmatic substance free of secretory material (fig. 3). In any area of a nuclear group, individual cells may exhibit wide variations in content of neurosecretory material (fig. 2). Occasionally, in the perikaryon as well as along the axon there may occur cytoplasmic swellings, Herring bodies, which exhibit a granular outer zone and a granule-free inner area (fig. 4). They are demonstrated (151) with special clarity in *Callithrix* (*Hapale*) (fig. 5). Where the fibers are less densely packed with neurosecretory material, they are often observed as distinct beaded threads (fig. 6). The amount of secretory material observed varies according to species and to the region of the system under investigation as well as its functional status. The posterior lobe (figs. 7, 11) always exhibits the greatest amount of neurosecretory material (24, 29, 84, 237). The demonstration and tracing of the neurosecretory pathways may be especially difficult in those forms (rodents) exhibiting little neurosecretory material proximal to the region of the tuber cinereum.

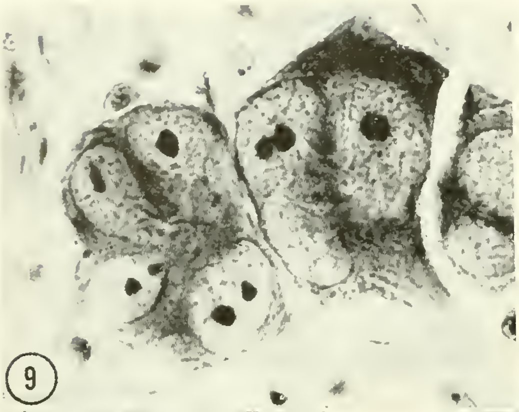
The similar intracellular localization of the Nissl material and the neurosecretory material, and the general inverse relationship which exists with respect to the relative content of these two substances (29, 164, 191), has led to the belief that the origin of the neurosecretory material is closely associated with the Nissl substance (286). Observations with phase contrast microscopy and embryological work do not support a strict correlation between the Nissl substance and the neurosecretory material (245, 340, 341).

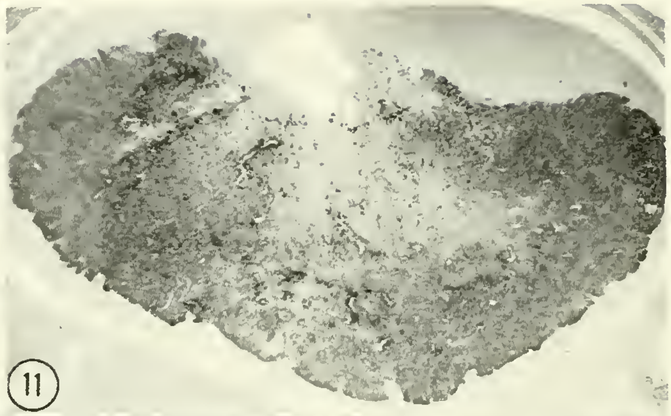
Differential centrifugation of beef pituitary homogenates has permitted accumulation of the neurosecretory material in a fraction with granules which range in size from 150 to 1.5 μ (292), with the particles having a tendency to aggregate in larger complexes. Electronmicroscopic observations of the neurosecretory material in the posterior lobe in reptiles, birds and mammals indicate that it consists of aggregates of granules which exhibit a surprising homogeneity with respect to size (100 to 300 μ) and density (34, 88, 89, 244). The range in size of these particles is approximately the same as that exhibited by mitochondria. The granules of the neurosecretory material do not stain with Janus green (292). The fraction of neurosecretory material obtained by centrifugation, however, does exhibit distinct reactions for succinic dehydrogenase, an enzyme considered to be associated almost entirely with the mitochondria. This biochemical determination correlates well with the histochemical demonstration of a rich content of succinic dehydrogenase in the posterior lobe of the white mouse (Ortmann, unpublished observations; fig. 7). To what extent the positive reactions obtained in both of these experiments are dependent upon the content of sulfhydryl groups in neurosecretory material and their reaction with formazan remains to be examined. Electronmicroscopy (34, 88, 89) as well as phase

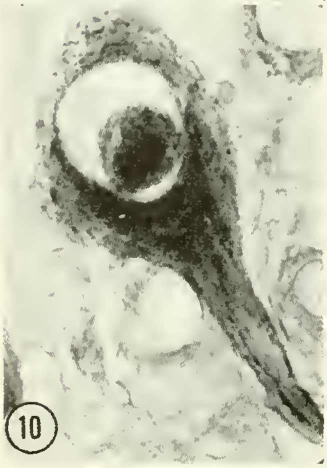
and join its fibers in the tract to the pituitary. The streamlined appearance of the Herring bodies in the *left fiber* corresponds to the direction of flow of material. Fibers containing all degrees of neurosecretory material are present. Chromhematoxylin-phloxin. × 195.

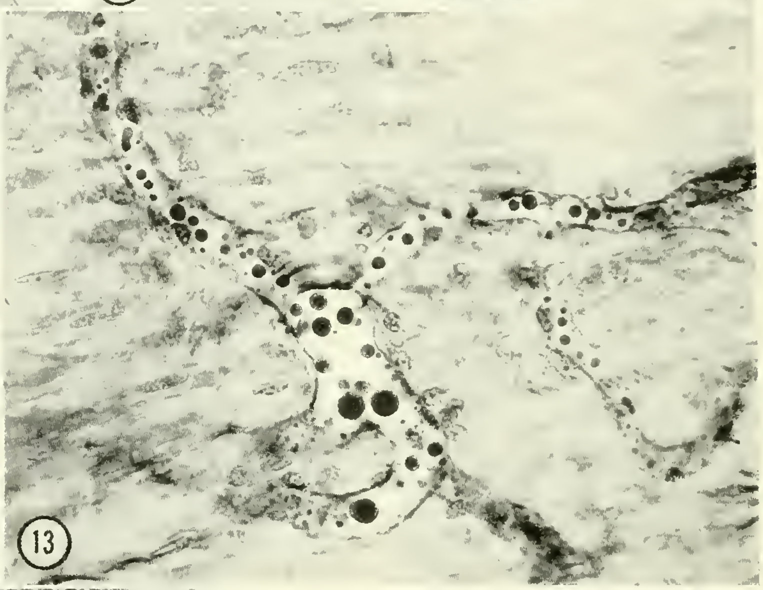
FIG. 7. Pituitary gland of the white mouse stained for the demonstration of succinic dehydrogenase. The enzyme activity is localized in the posterior lobe. Technique according to Ortmann (239). × 13.

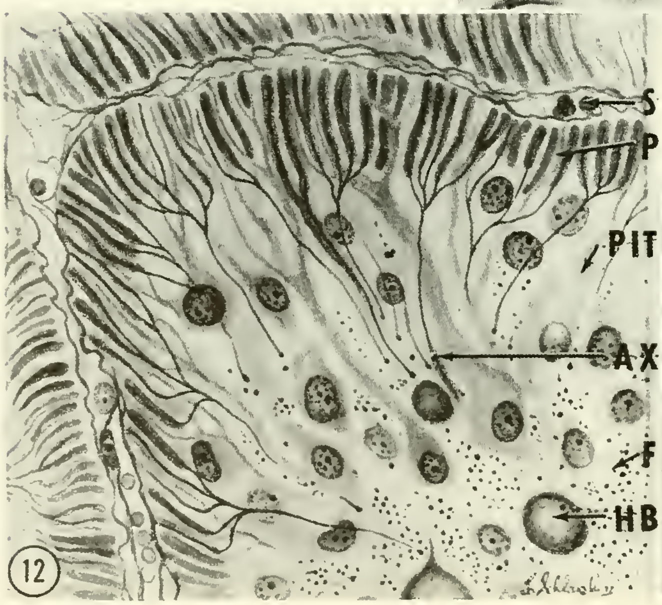
FIG. 8. Neurons from the supraoptic nucleus of the pigeon with large cytoplasmic colloid inclusions. Chromhematoxylinphloxin. × 1150. [From Bargmann & Jacob (33).]







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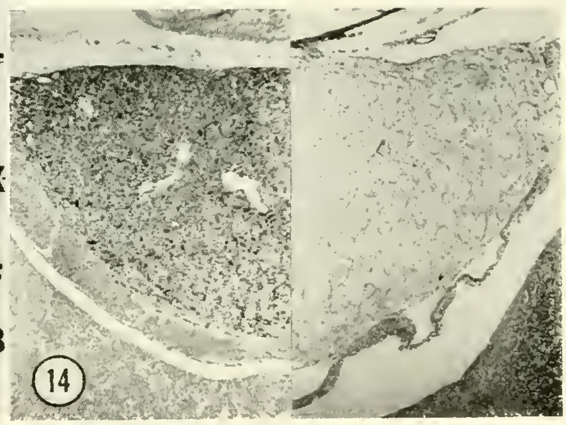


microscopy (245) permit a distinct differentiation between neurosecretory granules and mitochondria on the basis of density and structure. No final conclusion with respect to functional significance can be drawn from the close spatial relationship between mitochondria and neurosecretory material. Other electron-microscopic observations (134) indicate that in the region of the median eminence axons contain neurosecretory particles which are smaller than those found in the posterior lobe and may represent maturation stages.

In many species, colloid droplets exhibiting acidophilic staining properties (32, 37, 38, 289) as well as an affinity for chromhematoxylin (33, 214) are found in the cytoplasm and axons in addition to the characteristic neurosecretory material (fig. 8). It is noteworthy that although the colloid and granular neurosecretory material may be stained with chromhematoxylin, they exhibit significantly different histochemical reactions (294). Vacuoles are present also in the cytoplasm of neurosecretory cells, but their presence is so variable (164) that they may not represent a vital or functionally significant organelle (131, 243). In spite of this great variability, however, the presence of vacuoles in neurosecretory cells in both vertebrates and invertebrates is so widespread that it would seem their presence bears some relationship to the function of these cells. Further investigation must establish the significance of these vacuoles as well as the large nonstaining vesicles observed in neurosecretory cells of the dog and wolf (29, 153, 332). The latter may attain such size as to displace almost completely the nucleus (fig. 2) without seriously interfering with the secretory performance of the cell (172) or producing signs of cell degeneration. Verney (332) interprets these large vesicles as osmoreceptors, but their isolated occurrence in only a few species argues against this interpretation. Furthermore, experimental evidence (85, 172, 177) indicates that this is a reversible phenomenon dependent upon the functional status of the cell. The appearance and structure of the chondriome and Golgi apparatus in neurosecretory cells are similar to those observed in true glandular tissue (223, 309).

The functional status of neurosecretory cells is clearly reflected by changes in nuclear size (96, 101, 173, 237) as well as changes in the nucleoli (167, 188, 237), measurements used extensively as indices of cell activity (188, 224). In neurosecretory cells of fishes, villus-like processes as well as deep incisions of the nuclear membrane have been described (fig. 9) similar to those observed in the nuclei of glandular cells (238, 240, 281, 317). The delivery of small segments of the nucleus to the cytoplasm has been observed also in neurosecretory cells (163, 204, 238, 281, 296, 297), a fact suggesting a regular participation of the nucleus in the secretory activity of the cell. The significance of this is further emphasized by the fact that portions of these nuclear segments contain a granular or colloid-like material (fig. 10) which displays several of the staining reactions exhibited by neurosecretory material (30, 164, 199, 238, 310). The occasional presence of degenerating neurosecretory cells has been verified (61, 143, 144, 150, 151, 166, 301), but the hypothesis of a physiological degeneration of the cells as a necessary preliminary to synthesis of the neurosecretory material finds acceptance with only a small number of investigators (71, 142, 232, 303, 314).

The axons of neurosecretory cells do not all end in the posterior lobe but terminate also in the pituitary stalk as well as in the median eminence. In fish and

FIG. 9. Neurons from the posteroventral portion of the preoptic nucleus of *Cyprinus carpio*. Although the cells appear to be multinucleate, it can be shown that the several lobules are continuous. Iron-hematoxylin. × 840. [From Ortmann (238).]

FIG. 10. Neuron from the preoptic nucleus of *Cyprinus carpio*, showing a large nuclear inclusion. The cytoplasmic neurosecretory material and the granular part of the nuclear inclusion are stained with paraldehyde-fuchsin while the nucleolus is unstained. Paraldehyde-fuchsin. × 875.

FIG. 11. Section of the pituitary of the cat, with the posterior lobe darkly stained with paraldehyde-fuchsin while the intermediate and anterior lobes are almost colorless. The darkly-staining objects centrally located in the posterior lobe are Herring bodies. Note the accumulation of neurosecretory material around the blood vessels.

FIG. 12. Diagrammatic section of the posterior lobe of the opossum. The lobe is subdivided into numerous compartments by connective tissue septa along which the nerve terminations and blood vessels are in intimate contact. Nerve fibers of the hypophyseal tract (*F*), pituicyte cell bodies and three Herring bodies (*HB*) are shown in the hilum of the lobule (*lower right*). Surrounding this, the palisade zone (*P*) is seen to be formed by nerve fiber terminations coated with a rod-like formation of neurosecretory substance. Interspersed are pituicyte fibers (*PIT*) which extend to the vascular-collagenous septal layer (*S*). An axon (*AX*) about to form endings coated with neurosecretory substance is also visible. [From Bodian (55).]

FIG. 13. Capillaries in the neural lobe of the giraffe with numerous colloid droplets stained bright red with azan. [From Hanström (149).]

FIG. 14. Rat pituitary, showing a normal content of neurosecretory material in the posterior lobe (*left*) and its depletion after 14 days of water deprivation (*right*). Note the changes in size and structure in the depleted organ. Chromhematoxylin. × 50.

amphibia, as well as in mammals, an unbranched neuron may pass directly to the ependyma of the third ventricle in the area of its nucleus of origin or as far as the ventricular surface of the infundibulum and deliver neurosecretory material into the ventricular fluid (29, 39, 73, 163, 164, 214, 231, 243, 282). This phenomenon has been characterized as hydrencephalocrinie and may take the form of a holocrine secretion. This release of neurosecretory material into the third ventricle parallels the secretory activity in the rest of the system (164, 198), although no known significance can be attached to this phenomenon at present. Knowledge of the further fate of this material has been obtained by the demonstration of the neurosecretory material and antidiuretic substances in the plexus of the third ventricle (329). The typical termination in the wall of the infundibulum and in the posterior lobe is the Herring body with its inner and outer zones as described above (figs. 4, 5). The identification of these Herring bodies as degenerating cells or as cytoplasmic fragments with degenerating nuclei (141, 143, 144) is refuted by most investigators (32, 61, 134, 149, 151, 172, 243, 265). The question of whether neurosecretory material is deposited and is present in the interstitial space of the posterior lobe (that is outside the nerve fibers and their terminations) cannot be answered with certainty (fig. 11) (164). The problem cannot be resolved with light microscopy, while electronmicroscopic observations indicate that the neurosecretory material is restricted to the nerve terminations (34, 89, 244) or that it is present outside of them also (135, 139). The relationship of the posterior lobe pituicytes to the neurosecretory material has to date not been clearly defined by either light or electronmicroscopy nor by transplantation experiments. Notable amounts of neurosecretory material do not appear to be present in the pituicytes (89, 203). In the case of experimentally altered neurosecretory activity, the pituicytes do exhibit changes such as mitotic activity, changes in cell size, appearance of vacuoles, etc., which may indicate some functional relationship to this activity but which as yet do not define any specific role (165, 189, 237). A model of our conception of the nerve terminations of neurosecretory fibers is seen in the posterior lobe of the opossum where these structures are arranged in palisades closely associated with the capillaries in the connective tissue septa (55)(fig. 12). Green & van Breemen (134) hold that other tissue elements participate in the formation of these palisades. Bargmann (32) has confirmed the observation of Bodian that each nerve termination is surrounded by an accumulation of neurosecretory material. This palisade structure and the associated neurosecretory material is seen with some variation in other species also (32).

The direct transfer of neurosecretory material into the capillaries of the posterior lobe (fig. 13) has been described in several species (21, 148, 149, 285) and is observed readily, under experimental conditions, evoking a strong release of neurosecretory material (197). Electronmicroscopic studies in normal dogs could not establish the fact that neurosecretory material may penetrate the boundary between the nerve terminations and the perivascular spaces of the capillaries of the posterior lobe. The absence of a blood-brain barrier in the 'contact zones' (Spatz) of the posterior lobe, its stalk and the median eminence permits an unimpeded exchange of vital dyes and enzyme-reactive substances between blood and nervous system (239). The ease with which materials may be transferred from the blood vessels into the tissues in these areas makes it easier to accept the possibility of a transfer of substances (neurosecretory material) in the reverse direction (244). Of some importance is the consideration that neurosecretory material does not appear to be released from the nerve cell bodies into the capillary beds of the hypothalamic nuclei. Besides the fact that neurosecretory material has seldom been observed in the endothelium of the capillary bed (63), most of the experimental evidence speaks against the possibility of a depletion of the neurosecretory material in the region of the hypothalamic nuclei (165, 224, 237). In this connection there still remain unexplained the numerous observations that nerve fibers filled with neurosecretory material are present in the intermediate lobe (30, 32, 78, 98, 150, 151, 164, 233, 339) as well as in the anterior lobe (76, 233).

Increasing numbers of observations indicate that neurosecretory fibers of the hypothalamus may terminate in other areas of the central nervous system (8, 40, 81, 125, 164, 283). In the bat, five such areas have been described, including the amygdala, septal region and mesencephalon. In the mouse, termination have been observed in the wall of the lateral ventricles (39, 40), with similar findings being described in fish, amphibia, reptiles and birds (193, 194). No explanation is available for the function of these instances of 'neurocrinie de substances neurosécrétoires' (39). In animals treated with sugar an increased staining of these pathways was shown (194). Seasonal variations in the appearance of the supraopticohypophyseal system is particularly clear in the true hibernators (23, 24, 320), with storage of the

neurosecretory material in winter months and depletion in the summer. Earlier arousal of these species from the hibernating state leads to a more rapid depletion of the neurosecretory material (24). Species which do not remain in constant hibernation exhibit no variations with respect to the supraopticohypophyseal tract (22). Experimental hypothermia in dogs leads to no apparent changes in the neurosecretory material. In the chicken, much variation in the amount of neurosecretory material was observed at the time of ovulation as well as during nesting, with a particularly interesting differential response of the paraventricular and supraoptic nuclei (195).

ONTOGENY. The embryological maturation of neurons of the hypothalamoneurohypophyseal system is completed relatively late and partly only after birth (263). Although there is considerable species variation with respect to the initial appearance of neurosecretory material, it is generally observed first in the posterior lobe or simultaneously in the posterior lobe and in the hypothalamic nuclei and appears along the fiber tracts only at a much later time. In the chicken, it appears simultaneously in the supraoptic nucleus and the posterior lobe on the 14th day of incubation, with the paraventricular nucleus exhibiting material several days later (139, 340, 341). Another report (226) suggests a considerably earlier appearance of the neurosecretory material in the chicken. In the European Water Snake, neurosecretory material is demonstrated first in the posterior lobe 3 days before hatching, but not until 14 days after hatching in the supraoptic nucleus (164). A similar situation is observed in *Tinca* (163). Mammals exhibit little neurosecretory material at birth (29, 42, 79, 84, 134, 263, 284).

HISTOCHEMISTRY. Treatment of unfixed tissues with alcoholic solutions or fat solvents for 12 hours depletes completely the stainable neurosecretory material without removing the biologically active posterior lobe hormones (171). Extraction by these methods removes also those materials which give positive reactions for sulfhydryl groups (35). The solubility properties of the material extractable from the subcommissural organ appear to be fundamentally different (36, 340). After evaporation of the solvents, the granular nature of the extracted neurosecretory material is maintained (293) as well as its usual staining characteristics (164). From these observations, it would appear unlikely that the neurosecretory material can identify or represent the hormone content of these tissues. Sloper (300), however, has criticized the extraction methods used in those experiments which are claimed to demonstrate the differential solubility of neurosecretory material and the posterior lobe hormones. His observations indicate that lipids do not form an essential component of the neurosecretory material but that they probably play a role in binding the neurosecretory material to other tissue constituents. The relationship between the posterior lobe hormones and neurosecretory material awaits further elucidation. It was the subject of discussion by Acher (1) at a recent symposium.

Using the McManus periodic acid stain, Sudan black, Baker's acid hematin test, as well as the Millon protein reagent, Schiebler (293) came to believe the neurosecretory material to be a glycolipoid-protein complex. Sloper (300) feels that the carbohydrate-fat component is not an essential part of the neurosecretory material. The intensity of the McManus reaction is relatively weak in comparison to that exhibited by the colloid of the anterior and intermediate lobes and the basophils of the anterior and posterior lobe (25, 222). Ribonucleic acids do not constitute a significant component of the protein portion of the neurosecretory material in view of the fact that no changes are observed after treatment with ribonuclease (237, 293). Trypsin on the other hand destroys the neurosecretory material within 3 hours (300). Periodic acid cannot be substituted for potassium permanganate in the oxidation step of the chromhematoxylin staining method (293). It is believed that the presence of reactive aldehyde and sulfhydryl groups makes possible the key steps in the chromhematoxylin and aldehyde-fuchsin staining procedures (117).

In almost all cases the staining methods for sulfhydryl groups yield results parallel to those obtained with the usual staining procedures (35). After dehydration, for example, reactions for sulfhydryl groups diminish, paralleling the depletion of the neurosecretory material, while remaining unaffected in other areas of the nervous system. Another reaction for sulfhydryl groups, alcean blue following oxidation with performic acid (4, 5), is not destroyed after 24 hours of extraction of tissues in hot chloroform-methanol. The staining in this case depends upon the oxidation of sulfhydryl groups to sulfonic acid groups, and in view of the fact that oxytocin contains 19 per cent cystein, this reaction may be almost specific for posterior lobe hormones. The sensitivity of neurosecretory material to tryptic digestion, together with the fact that its staining properties are lost after

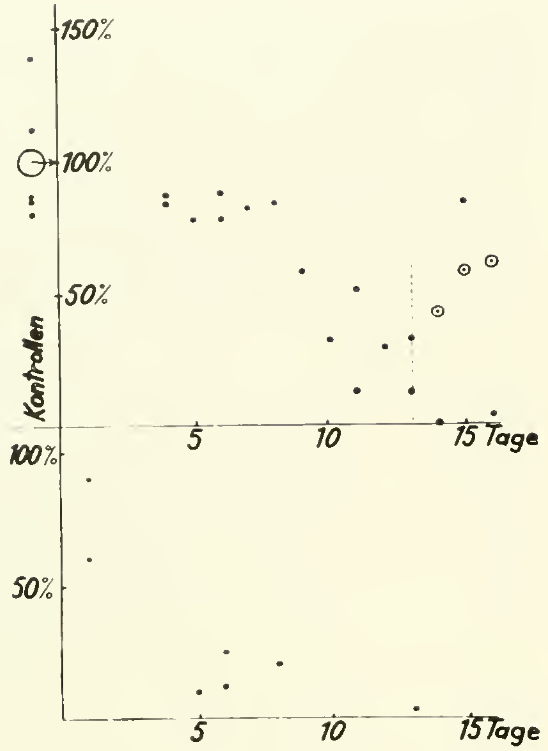


FIG. 15. Correlation between content of neurosecretory material and antidiuretic hormone in the posterior lobe following water deprivation. In the *upper figure* is plotted the content of neurosecretory material expressed as per cent of the mean control value set at 100 per cent. [From Ortmann (237).] The *lower graph* is plotted in the same manner, showing the content of antidiuretic hormone. [From Hickey (162).]

treatment with homogenates of liver, spleen, lung, kidney and striated muscle, also suggests this conclusion (45, 103). Numerous elements in the hypothalamic nuclei concerned with neurosecretory activity exhibit pronounced phosphatase activity (26, 102, 292).

EXPERIMENTAL STUDIES. On the basis of changes in the histologically demonstrable neurosecretory activity, several experimental procedures have contributed importantly to an understanding of the functional significance of this system. These have been: *a*) conditions which lead to marked but usually reversible depletion of the neurosecretory material and to characteristic morphological changes in the constituent elements of this system (237); *b*) stalk section experiments which yield information about the sites of production and delivery of the neurosecretory material (165); and *c*) the application of assay methods for posterior lobe hormones under experimental conditions which have demonstrated clearly the relationship between these and the neurosecretory system (168–172, 343, 344). The basic premises derived from these several methods of investigation have been confirmed repeatedly and may be considered as definite and basic facts. Specific details of notable studies will be enlarged upon in the following paragraphs.

Dehydration, thirst, overloading with sodium chloride and heat have been proved to be the condition for depletion of neurosecretory material (237). Similar changes are produced by stress (264), adrenalectomy (97), alloxan diabetes (189) and some drugs (55, 285). Many workers have studied these conditions in widely different species and by various methods (5, 16, 17, 26, 54, 82, 121, 134, 165, 172, 187, 188, 191, 199, 202, 234).

The effects of depletion of neurosecretory material appear first in the posterior lobe (figs. 14, 15), with the finely granular neurosecretory material disappearing first. In spite of extensive depletion of the neurosecretory material, some Herring bodies in the hypothalamic nuclei as well as in the posterior lobe may remain unaffected for a considerable period of time (237). The length of time required to deplete the neurosecretory material varies considerably according to the species investigated and the methods employed. Thirst produces this effect in the rat in 12 to 14 days and in the dog in 7 to 14 days, while stress may deplete the neurosecretory material in the rat within 10 min. (17, 35). Concomitant with depletion of the neurosecretory material there occur the following changes in the neuron cell body: nuclear enlargement (96, 173, 211), eccentric displacement of the nucleus, enlargement of nucleoli (figs. 16, 17), dissolution of the Nissl material and eventual degeneration of the cell (fig. 16*C*). Mitotic activity of posterior lobe pituicytes is pronounced in the rat (237) and frog (165), but only minimal in the dog (172). Up to the point of cell degeneration, all of these changes are reversible. It should be pointed out that each of these cellular changes is similar to the axon reaction and may represent an increased nervous activity as well as secretory activity of the cell. The fact that these cellular changes are reversible indicates also that the occasional presence of degenerating cells is not to be taken as an essential index of the status of secretory activity. The length of time required for the complete reaccumulation of the neurosecretory material is generally longer than that required to cause the preceding depletion. Chronic administration of saline drinking water leads to an increased content of neuro-

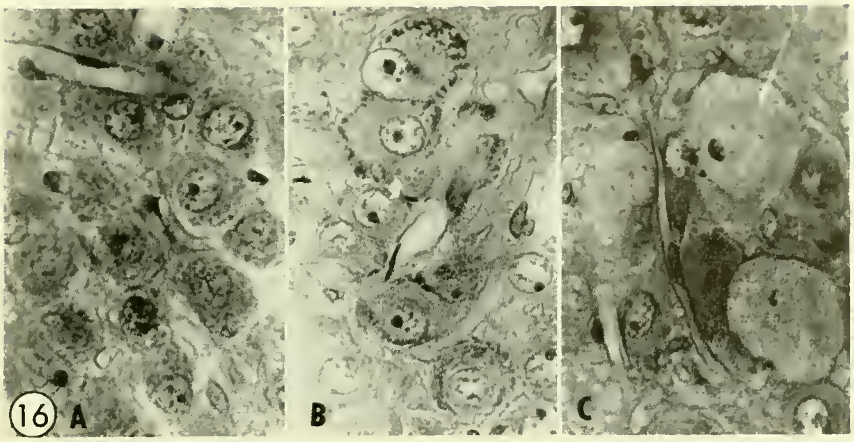


FIG. 16. Supraoptic nucleus of the rat; *A*, normal; *B*, after 15 days of water deprivation, showing increase in size of the nuclei and nucleoli and peripheral disposition of the Nissl substance; *C*, degenerating neuron seen after two injections (3.6 per cent of the body weight) of 5 per cent sodium chloride. Chromhematoxylin-phloxin. × 470.

secretory material in all segments of this system, a finding interpreted as an adaptation with subsequent hyperfunction.

Transection of the supraopticohypophyseal tract has been carried out with many variations (46, 172, 179, 191, 215, 224, 290, 316, 317) and leads to an accumulation of neurosecretory material proximal to the cut (fig. 18*A*), while distal to the section (fig. 18*B*) only a depletion of the neurosecretory material is observed (86, 165, 172, 215, 316, 317). After transection of the stalk, the neurosecretory material in the posterior lobe is removed only slowly, even under those conditions which normally evoke a rapid depletion (165). Correspondingly, if the posterior lobe is first depleted of neurosecretory material, it will remain so after transection of the tract. In the usual transection experiments, the region proximal to the cut accumulates a content of neurosecretory material which is far greater than ever observed under normal conditions. A similar situation of accumulation of neurosecretory material has been observed in man when obstructive tumors block the neurosecretory pathways (227). Three to four weeks after hypophysectomy of the rat, the infundibular stump undergoes changes which resemble a regeneration (fig. 19), including a rich vascularization of the reorganized glial material and subsequent accumulation of neurosecretory material (122, 124, 179, 290, 316, 317). This depot of neurosecretory material can be experimentally depleted but only under intensive stimulation such as simultaneous salt load and administration of desoxycorticosterone (46). These findings may explain some of the consequences of hypophysectomy observed experimentally as well as clinically. The remission of diabetes insipidus following hypophysectomy, for example, may be correlated with

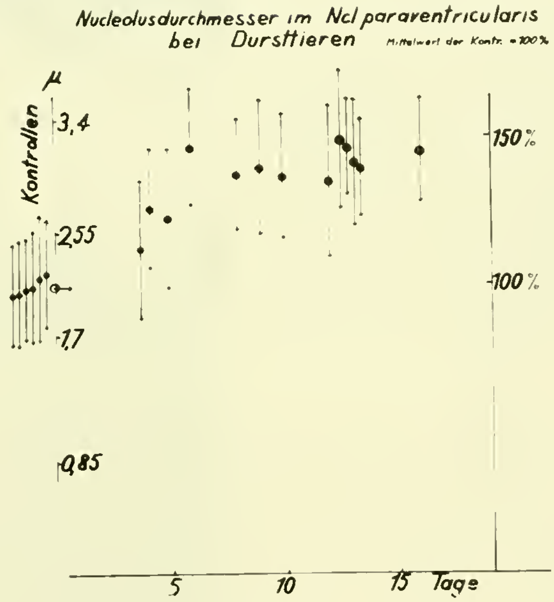


FIG. 17. Graph of nucleolar size in neurons of the paraventricular nucleus of the rat following water deprivation. [From Ortmann (237).]

the renewed secretion of antidiuretic hormone from the infundibular stump (177). In the toad, a true regeneration of fibers of the preoptic-hypophyseal tract has been described (180).

The experiments of Hild & Zetler (168–172, 343, 344) indicate that the content of neurosecretory material is closely correlated with the hormone content in the posterior lobe (figs. 20, 21). These were confirmed by other workers (6, 26, 67, 82, 225, 285, 333). In all species studied, those areas of the nervous system which contain posterior lobe hormones always contain neurosecretory material also. These areas

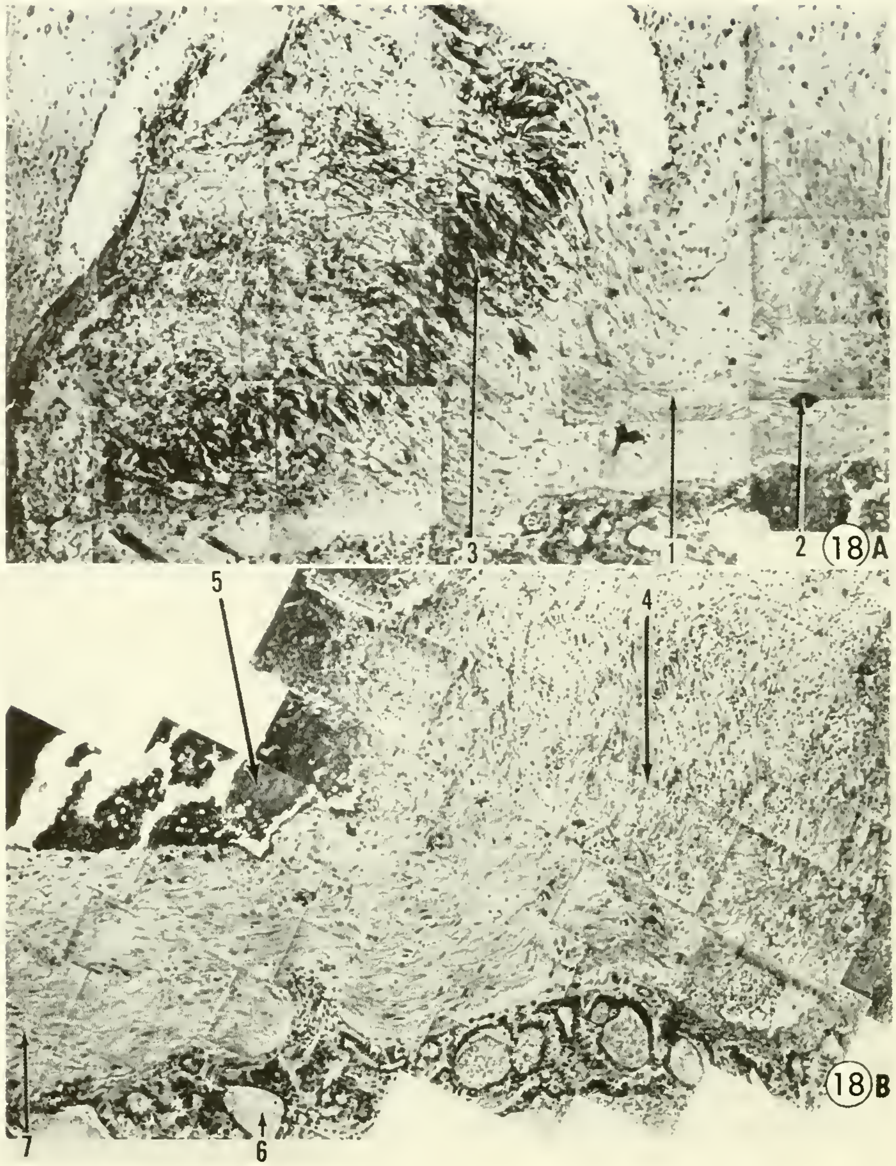


FIG. 18. Neurosecretory material in the central (*A*) and distal (*B*) segments of the supraopticohypophyseal tract of the dog after dissection of the tract *in vivo*. In the central segment (*A*), the fibers appear to be of normal size (*1*), numerous Herring bodies are present (*2*) and a large amount of neurosecretory material has accumulated (*3*). In the distal segment (*B*), the fibers are swollen and contain no neurosecretory material (*4*). A blood clot (*5*), colloid follicles of the intermediate lobe (*6*) and transition area of the stalk into posterior lobe (*7*) can be seen. Chromhematoxylin-phloxin. [From Hild & Zetler (172).]

include the supraoptic and paraventricular nuclei, the fiber tracts of these nuclei into the tuber cinereum and the infundibulum as well as in the posterior lobe (figs. 20, 21; table 1).

The contents of neurosecretory material and posterior lobe hormones parallel each other closely during ontogenetic development. Newborn mammals contain very little neurosecretory material and a paucity of antidiuretic hormone and exhibit the so-called physiological diabetes insipidus (29, 42, 79, 83, 156, 263). Posterior lobe hormones are demonstrable in the chicken at 9 to 10 days of incubation, whereas the neurosecretory material appears first at 13 to 14 days (340), a discrepancy which may be due to greater sensitivity in detecting the former substance.

There are marked differences in the amount of both the hormones and the neurosecretory material which are due to different species, various regions of the neurosecretory system and individual variability. Nevertheless, the contents of the hormones and neurosecretory material always correlate closely (table 2). In the dog and cat, the hormone and neurosecretory material content of the hypothalamus is particularly rich. Under a wide variety of experimental conditions, the neurosecretory material and posterior lobe hormones exhibit parallel changes in content (table 3).

Stainable neurosecretory material as well as maximal amounts of the oxytoxic and vasopressor hormones may be obtained from the same granule fraction of posterior lobe homogenates (132, 246, 292). The reports of an increase in neurosecretory material in the supraoptic and paraventricular nuclei after potassium cyanide poisoning (129) and hypoxia (259) require confirmation.

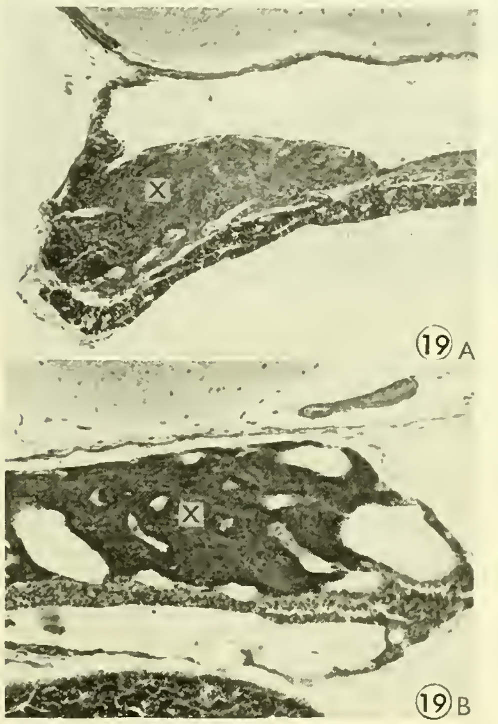


FIG. 19. *A*, cross-section of the regenerated neural lobe of a toad 6 mos. after hypophysectomy and autotransplantation of the pars distalis; *B*, cross-section of a normal neural lobe (*X*). Note the sinusoid vessels in the regenerated lobe. Gomori staining method. × 65. [From Jorgensen *et al.* (179).]

Attempts to transplant or culture hypothalamic or posterior lobe tissue have not been particularly successful. Although cultured nerve fibers of the hypothalamus (even from adult tissue) may exhibit remarkable growth, direct evidence of secretory activity could not be demonstrated by either staining methods or by attempts to extract hormones (167). The observed transport of particles along the axon cannot be considered as specific evidence of secretory activity in view of the fact that this phenomenon occurred in both directions along the axon as well as the fact that cultures from other regions of the nervous system were observed to behave similarly (126). The efforts to demonstrate hormone secretion in posterior lobe cultures (123, 134) are considerably handicapped by the large amount of hormone already present in the tissue at the time of explantation (167). With repeated subculturing of posterior lobe tissue, hormone (as well as neurosecretory material) can no longer be demonstrated (167). This, however, may be due to lack of innervation to the pituicytes as well as to their progressive dedifferentiation to protoplasmic astrocytes.

FUNCTIONAL RELATIONSHIPS. In spite of some objections (87, 131, 144, 314), it seems clear that a close relationship does exist between the neurosecretory material and the so-called posterior lobe hormones which have been well defined chemically (2). The suggestion to rename the posterior lobe hormones as 'hypothalamus hor-

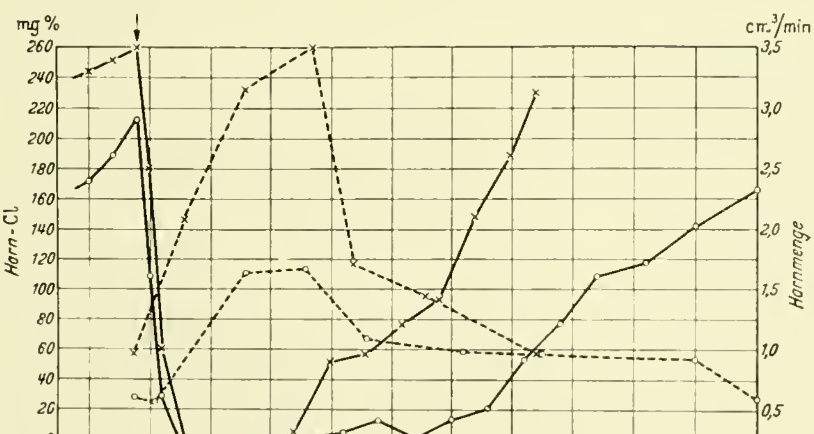


FIG. 20. Evidence of antidiuretic and chloride-concentrating action of extracts of hypothalamic nuclei of the dog. Two hours before urine collection, 100 cc of water is administered by stomach tube, with an additional 300 cc at the beginning of collection. After a diuresis of 2 to 3 cc per min. is established, the extract of supraoptic or paraventricular nucleus is injected intravenously in a dose corresponding to a 4 × 10^5 part of the nucleus. Urine flow (x—x—x) and chloride concentration (x---x---x) measurements are shown after injection of extracts of the supraoptic nucleus, urine flow (o—o—o) and chloride concentration (o---o---o) after injection of extracts of the paraventricular nucleus. [From Hild & Zetler (168).]

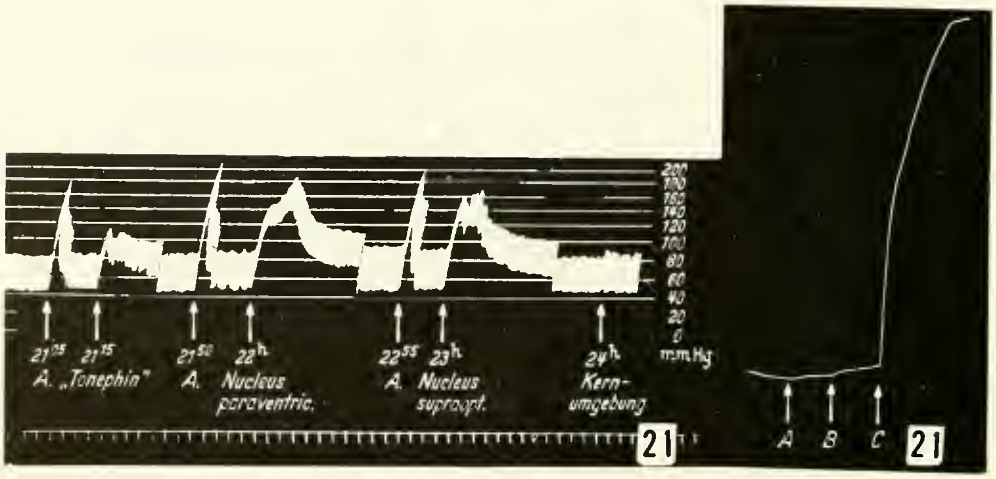


FIG. 21. *Left.* Arterial pressure record of a decapitated cat following injection of epinephrine, posterior lobe extract ('Tonephin'), extracts of the dog paraventricular and supraoptic nuclei, and an extract of nervous tissue not including these nuclei ('Kernumgebung'). *Right.* Record of the contraction of the isolated virgin guinea pig uterus. Extracts of nervous tissue not including supraoptic or paraventricular nuclei were added to the Tyrode solution at *A* and *B*. At *C*, an extract of the dog supraoptic nucleus corresponding to 0.196 mg of dry tissue was added. [From Hild & Zetler (168).]

TABLE 1. *Mean Absolute Content of Posterior Lobe Hormones in Several Segments of the Supraopticohypophyseal Tract of 10 Dogs*

Condition	Supraoptic Nucleus			Paraventricular Nucleus			Tuber Cinereum			Posterior Lobe		
	A	V	O	A	V	O	A	V	O	A	V	O
Normal	0.61	1.13	0.63	0.31	0.64	0.10	1.29	1.34	0.21	13.8	19.98	6.64

Relative content of posterior lobe hormones in several segments of the supraopticohypophyseal tract following water deprivation and rehydration; values are expressed as per cent of the content in normal dogs (10 animals were present in each group).

Thirst, days	Rehydration, days												
8		29.5	36.3	19.8	46.4	131.0	92.0	17.0	79.0	79.5	15.1	24.3	70.8
14		18.0	15.6	19.2	21.6	18.3	29.0	6.7	16.4	22.4	7.4	14.0	43.4
14	0.5	28.7	23.2	39.0	26.1	26.8	58.0	6.7	15.9	20.0	3.9	14.4	61.2
14	1.0	13.3	17.1	38.0	20.5	11.4	39.0	7.0	8.9	24.3	7.3	21.2	79.3
14	4	22.2	23.2	28.3	29.7	13.4	57.0	15.4	14.0	52.0	17.0	72.1	97.0
14	4*	53.3	32.5	39.7	32.3	30.0	92.0	52.3	178.3	300.0	7.3	13.7	16.1
14	8	36.0	31.3	27.2	31.0	37.3	45.0	9.2	9.2	19.0	34.9	85.0	81.3

A, antidiuretic hormone; V, vasopressin; O, oxytocin.
* Supraopticohypophyseal tract transected after the 14 days of water deprivation. From Hild & Zetler (172).

mones' (Bargmann) should be at least temporarily discouraged, particularly since it has not been fully established that the posterior lobe is simply a depot for hormone and since the role of the pituicytes in the release of hormone is not clarified.

The interpretation of the stainable neurosecretory material as a carrier substance has received considerable support. Several considerations, however, are difficult to harmonize with this hypothesis; *a*) the almost identical content of sulfhydryl groups in

neurosecretory material and in the posterior lobe hormones suggests a far closer relationship than simply that of a carrier substance, *b*) it is not clear why the carrier substance is released into the blood stream also, and *c*) it is not clear why the carrier substance should be subsequently demonstrable as posterior lobe hormone (340). These questions and the histochemical results of Sloper become clearer on the supposition of an identity between the neurosecretory material and the posterior lobe hormones. See also the more recent discussion by Acher (1).

There can no longer be any doubt that neurosecretory material and the posterior lobe hormones are produced by nerve cells in the hypothalamic nuclei and that these substances are transported along the axons in fiber tracts passing to the posterior lobe of the pituitary. It is not clear why certain species do not store neurosecretory material in the hypothalamic nuclei and why specific segments of the neurosecretory pathways are completely devoid of this material. This latter observation has led several investigators to deny the axonal transport of neurosecretory material (84, 304). This concept has also been challenged on the basis that for simple physical reasons the axon would be unable to move or press such material along its length. The dynamic fluidity of cytoplasm as demonstrated by photography of tissue culture preparations contradicts such purely physical objections.

Estimation of the status of neurosecretory activity cannot be made solely from a knowledge of the amount of neurosecretory material present. Subnormal amounts of neurosecretory material may represent either a condition of lowered functional activity or accelerated release of neurosecretory material associated with hyperactivity. Hyperactivity is indicated clearly when a decreased content of neurosecretory material is associated with cytological evidence of increased cellular activity.

Only meager information is currently available with respect to the electrical activity in neurosecretory fibers. Several considerations indicate that such fibers should be capable of impulse conduction and possess excitatory capacity. Injection of hypertonic saline into the carotid artery is followed, after a very short latent period, by release of antidiuretic substance into the blood stream (184, 332) with simultaneous increased electrical activity in the supraoptic nucleus (228). Furthermore, the release of hormones from the posterior lobe is dependent upon the continuity of fibers in the stalk. The conductional capacity of neurosecretory fibers has been demonstrated in vertebrates by Potter & Lowenstein (258) and in invertebrates by Milburn [quoted by Bliss (49)].

The exact mechanism of release of posterior lobe hormones, as well as the role of the pituicytes, awaits further investigation. Research in neurosecretion has led to a fundamentally new interpretation of the function of the posterior lobe, namely that it serves only as a depot or reservoir for the posterior lobe hormones (165, 237). Hormones are released from this depot according to the needs of the organism. The release or depletion of hormones from this depot, requiring intact nerve connections (165), occurs considerably more rapidly than its reaccumulation (17, 237, 317). Although it is fairly certain that the pituicytes do not synthesize the posterior lobe hormones, it seems clear that they are concerned somehow in the mechanism of release (46, 124, 165, 179, 189,

TABLE 2. *Content of Posterior Lobe Hormones in the Hypothalamus Expressed as Per Cent of the Total Amount Present in the Corresponding Pituitary Gland*

Species	Posterior Lobe Hormones		
	Vasopressin	ADH	Oxytocin
Dog*	15.6	17.3	10.1
Dog†	25.8	24.3	2.27
Human*	2.0	1.3	2.5
Pig*	0.63	0.36	0.52
Ox*	0.23	0.24	0.28
Camel†	0.41		1.23

* From Hild & Zetler (170).
† From Adamsons *et al.* (6).

TABLE 3. *Studies Correlating the Alteration in Neurosecretory Material and Posterior Lobe Hormones Under Various Experimental Conditions*

Experimental Condition	Neurosecretory Material*	Analysis for Posterior Lobe Hormones*
Thirst	26, 35, 88, 165, 199, 237, 328	26, 162, 218, 299
Sodium chloride administration	16, 35, 165, 202, 216, 237	67, 68, 190, 262
Stalk sectioning	35, 46, 165, 172, 191, 316, 317	53, 225, 273, 330
Stalk regeneration	46, 179, 316	205, 206, 207
Stress	35, 265	67, 221
Adrenalectomy	97, 187, 191, 266	67
Pregnancy and lactation	74, 87, 212, 319	83, 181

* Numbers indicate text references.

237, 261). Complete elucidation of the normal relative content of the individual posterior lobe hormones in the different segments of the system (6, 168–171, 235, 315, 333) as well as their alteration under experimental conditions (3, 172) requires further cooperative research between the morphologists, chemists and pharmacologists. A conclusion with respect to any individual posterior lobe hormone based upon content of neurosecretory material must be drawn with considerable caution. Although the hormones appear to be secreted together even if not always in the same relative proportion, it is important to note that conclusions based upon alteration in the content of neurosecretory material represent only the sum of the components of the posterior lobe hormones.

In spite of one objection (87) it is evident that parturition and lactation lead to changes in the amount of neurosecretory material (21, 74, 212, 318). No explanation is available for relations between neurosecretory activity and reproductive behavior (193, 195, 198, 199, 217, 307, 338).

Reflex release of posterior lobe hormones leads to a secretion of both oxytocin and antidiuretic hormone (155, 230). Injections of hypertonic solutions into the internal carotid lead to secretion of antidiuretic hormone but also produce milk flow and increased uterine motility through release of oxytocin. The suckling stimulus produces an antidiuresis as well as milk ejection. Coitus leads to increased uterine motility as well as simultaneous milk ejection and antidiuresis. Electrical stimulation of the supraoptic and paraventricular nuclei of the goat leads to simultaneous release of antidiuretic hormone and oxytocin (10). Osmotic stimulation from the carotid artery leads to increased electrical activity in the supraoptic region (228). The observation of Pickford (254) that acetylcholine injected into the carotid artery leads to antidiuretic hormone secretion suggests that stimulation of the cells of the supraoptic nucleus occurs throughout chocinergic synapses. The role of neurosecretory pathways is further indicated by the evidence of thirst centers in the hypothalamus. By microinjection of sodium chloride, by electrical stimulation (in the goat) or by production of suitable hypothalamic lesions in the dog (9–11), specific thirst centers can be demonstrated. The polydypsia produced by these methods may be associated with changes in antidiuretic and oxytocic hormone or with other nervous pathways leading to increased diuresis (12). The relationship of the posterior lobe and its hypothalamic connections to the condition of diabetes insipidus has been extensively investigated (104, 105, 184, 263, 332). Chamorro and co-workers (69, 70) succeeded in demonstrating the release of antidiuretic hormone and oxytocin after brief stimulation with application of epinephrine solution to the frontoparietal region of the cortex. Interestingly, hormone secretion was observed after this stimulus even following hypophysectomy.

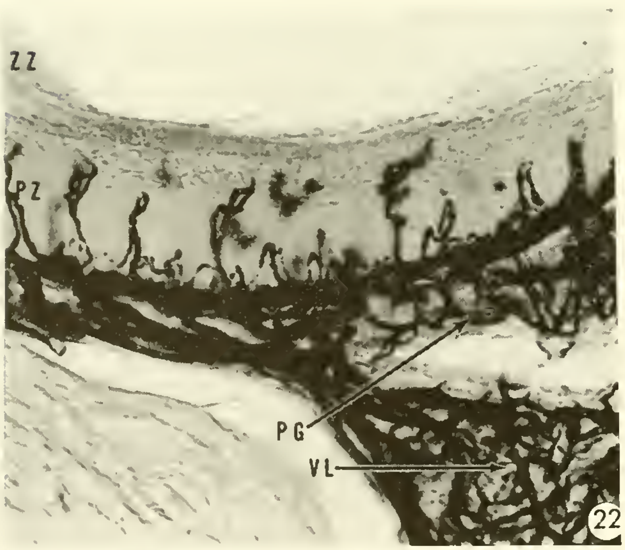
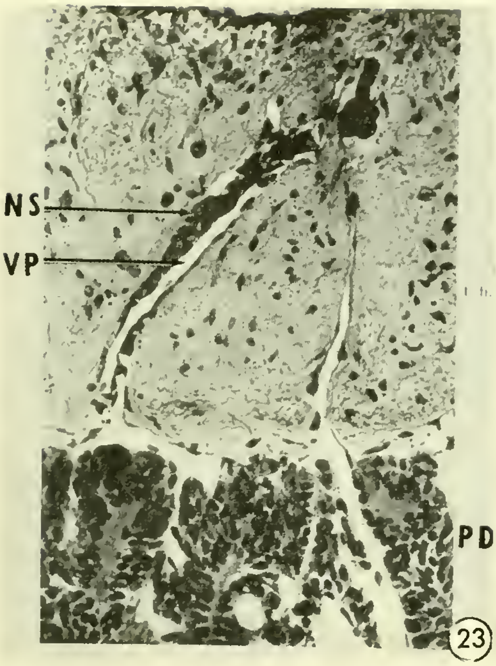


FIG. 22. Capillary loops from the portal vessels projecting upward into the central (*ZZ*) and peripheral (*PZ*) zones of the wall of the infundibulum. *PG*, portal vessels draining into the anterior lobe, *VL*. Injection preparation from Engelhardt. × 90. [From Engelhardt (100).]

Recent evidence suggests that neurosecretory activity of the supraoptic and paraventricular nuclei may be concerned in the control of ACTH release and, therefore, in the control of adrenal cortical function. Administration of adrenal cortical hormones as well as adrenalectomy leads to evidence of increased neurosecretory activity (28, 97, 187). Thirst and sodium chloride treatment, while producing heightened neurosecretory activity, lead also to morphological changes in the adrenal cortex (77, 97).

A humoral link between the hypothalamus and the adenohypophysis traversing the pituitary portal vessels has been sought for some time. In the region of the median eminence (figs. 22, 23), fibers of the supraoptical hypophyseal tract assume an especially close relationship to the primary plexus of the portal vessels (29, 31, 35, 243, 284, 316). Stalk section as well as appropriate lesions in this area has shown quite clearly the significance of these portal vessels (46, 205, 206, 220). A transfer of stainable neurosecretory material into the portal vessels has been observed histo-



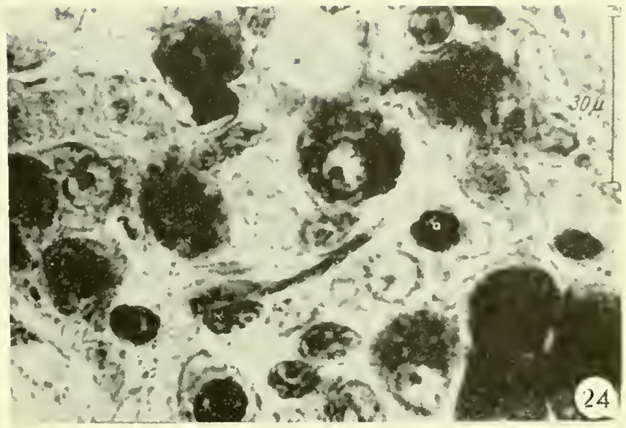


FIG. 23. Portal vessels (*VP*) in the wall of the infundibulum in close relationship to neurosecretory fibers (*NS*) of the supraopticohypophyseal tract of the dog. The pars distalis (*PD*) is shown below. [From Scharrer (284).]

FIG. 24. Neurosecretory a-cells from the brain of *Lumbricus terrestris*. *Centrally* the two cells appear vacuolar while those at the *lower right* are full of neurosecretory material. Azan stain. [From Hubl (176).]

logically (193, 264), while neurosecretory-like material has been found in the cells of the pars tuberalis (193, 197, 224). A basic requirement for such hypothalamic control of adenohypophyseal function is that the direction of blood flow in the portal vessels be from the hypothalamus to the pituitary. This has been shown by direct observations of the portal vessels of various amphibia (133), the rat (135, 342) and the dog (178, 327).

Several investigations (35, 264) have shown that stressful conditions produced marked morphological changes in the neurosecretory system. It has further been shown that the release of ACTH is dependent upon the integrity of the supraopticohypophyseal tract as far as the median eminence, while the subsequent course of this pathway from the infundibulum into the posterior lobe is not necessary for ACTH secretion (209). Suomalainen (320) believes that the seasonal variation in activity in the hypothalamic pituitary system in the hedgehog is related partly to varying ACTH need. Kovacs and co-workers (188), however, feel that no relationship exists between hypothalamic nuclei and ACTH control. ACTH release is evoked only by high doses of posterior lobe extracts (298). Posterior lobe hormones can release ACTH from pituitary glands transplanted to the anterior chamber of the eye (213). Pituitary portal blood collected from the dog is capable of stimulating increased ACTH secretion in the rat (256). Attempts to isolate the active hypothalamic principle collected in such portal blood suggest that it is a high molecular weight protein similar but not identical to vasopressin (257).

Cultures of anterior lobe tissue which lose their ACTH activity in several days can be stimulated to renewed ACTH secretion by the addition of hypothalamic extracts (140). The active hypothalamic principle is not histamine, acetylcholine, epinephrine, norepinephrine, 5-hydroxytryptamine, oxytocin or vasopressor substance. An ACTH-stimulating factor has been isolated from posterior lobe extracts and shown by paper chromatographic methods to be distinctly different from vasopressin or oxytocin (269). This ACTH-stimulating factor has peptide properties and occurs as a contaminent of vasopressin. These observations explain the high doses of posterior lobe

extracts required to produce ACTH release. The activity of this partially purified substance can be demonstrated both *in vitro* and *in vivo*. A synthetic lysine-vasopressor substance has been reported to produce increased adrenocortical hormone secretion (210).

The morphological, chemical and experimental results obtained from these different laboratories agree to the extent that a specific substance is concerned in stimulating ACTH release. Its close relationship with the posterior lobe hormones, their sites of synthesis and storage, make it seem likely that the neurosecretory system plays a role in the formation and delivery of this hypothalamic substance.

Central Nervous System Neurosecretory Systems not Demonstrated with Chromhematoxylin

ANTERIOR HYPOTHALAMUS. In this area of the hypothalamus exist a large number of cells which contain granular and colloid inclusions not staining with chromhematoxylin or paraldehyde fuchsin (37, 38). The functional significance of this material is not clear.

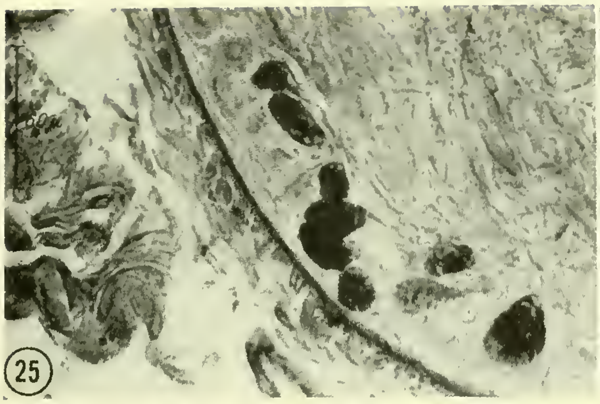
TUBER CINEREUM. In many species of fish, specific indication of neurosecretory activity is found in the lateral tuberal nuclei (38, 240, 280, 282, 302, 308) although with isolated exceptions (191, 302) the secretory material in these cells is not stained with chromhematoxylin (30, 128, 131, 163, 232, 307, 317). In lower forms, an evident participation of the nuclei in secretory activity as well as seasonal variations of activity is particularly characteristic for the cells in these tuberal nuclei (44, 105, 131, 163, 281, 282). In man, cytoplasmic colloid and granular inclusions as well as unusual nuclear shapes have been described for the cells in the tuberal nuclei (128, 255, 345); however, no evidence of axonal transport of secretory material is present. In mammals, axons from the tuberal nuclei, especially the nucleus infundibularis tuberis (arcuate nucleus), nucleus principalis (Cajal) and the posterior periventricular tuberal region, form the tuberohypophyseal tract, and in the region of the median eminence assume a close relationship to the primary plexus of the portal vessels. The terminations of these fibers lie superficial to the area traversed by the supraopticohypophyseal tract.

The question of whether these axons of the tuberal nuclei release a neurosecretory substance into the portal vessels cannot be answered with certainty at this time (44, 346). A colloid material which does not stain with chromhematoxylin has been observed in the median eminence (149, 339) as well as within the portal vessels. This may be an indication of a second form of neurosecretion, released into the blood stream in this area and traversing the portal vessels to the anterior lobe of the pituitary (157). Through measurement of nuclear volume as an index of cellular activity, the periventricular, ventromedial and premammillary hypothalamic nuclei have been identified as regions which undergo characteristic changes paralleling the phases of the reproductive cycle of the mouse (160, 161). It has been suggested that their function may be similar to that of the anterior hypothalamic areas (174). A notable array of experimental and clinical evidence indicates that considerable hypothalamic control exists over the gonadotropic activity of the anterior lobe (20, 43, 44, 122); this is discussed in the chapter in this work by Sawyer on reproductive behavior.

SPINAL CORD. The discovery of gland-like cells in the spinal cord of fish by Dahlgren (75) and Speidel (305, 306) forms the first description of neurosecretion but paradoxically has remained unexplained from a functional standpoint. Speidel has described these peculiar variations of the anterior horn cells only in the caudal segments of the spinal cord in 26 out of 30 species of fish in the elasmobranchs, teleosts and ganoids. The cells may be unusually large (200 x 200 x 176 μ) and contain nuclei which are lobular or even distorted in shape. The cytoplasm of these cells contains a variable accumulation of proteinaceous granules or colloid droplets which are Millon-positive (305) but which do not stain with chromhematoxylin (289). Similar observations have been presented recently for cells in the lumbosacral segments of the cord of various species of birds (271, 321). See also Sano (272).

Neurosecretion in Peripheral Nervous System

Lenette & Scharrer (201) have described cytoplasmic inclusions in autonomic ganglion cells of the monkey and have interpreted these findings as evidence of neurosecretory activity. Similar observations were subsequently presented for the cells of a variety of mammalian species including ganglion cells of the sympathetic chain (95, 219, 291, 295), uterine cervix (200, 311, 312) and adrenal medulla (94, 251, 252). Vacuoles and colloid droplets may accumulate in these cells to such a degree as to produce visible swelling of the cell without producing any evidence of nuclear or cytoplasmic damage or degeneration.



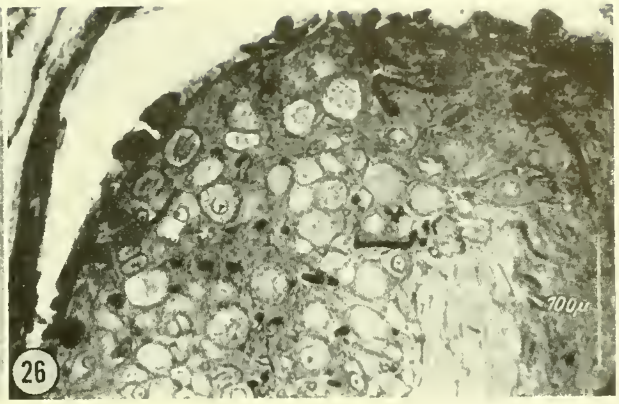


FIG. 25. Neurosecretion-rich cells (μ-cells) from the subesophageal ganglion of *Lumbricus*. The cell processes are visible in some cases. Paraldehyde-fuchsin stain. [From Hubl (176).]

FIG. 26. Neurosecretory cells in the brain of *Lumbricus* after sectioning of the nerve cord. The vacuolated appearance of the c-cells is believed to reflect heightened functional activity. Azan staining. [From Hubl (176).]

Specific staining methods for demonstrating the secretory products of these cells are not available. The nuclei frequently exhibit evidence of participating in the secretory activity of these neurons (296, 297). In the pregnant rat, neurons of the uterine cervix ganglion exhibit increased vacuolation (200). Similar changes have been described following treatment with estrogens and chorionic gonadotrophins (311). Pilocarpine accentuates while atropine restricts the secretory activity of these cells (312). In spite of many such studies, the functional significance of neurosecretory activity in peripheral neurons is not clear. Likewise, the attempts to ascribe neurosecretory activity to certain neurons of the retina (41) must be considered with some reservation.

NEUROSECRETION IN INVERTEBRATES

General Considerations

Although neurosecretory elements are demonstrated easily in invertebrates with routine staining methods (fig. 24), the application of chromhematoxylin and paraldehyde fuchsin (fig. 25) has substantially advanced our information in this domain. The use of these methods has permitted differentiation of several closely localized neurosecretory products. It is characteristic of a large number of invertebrates that neurosecretory axons terminate intercellularly in glands which, in turn, are themselves secretory in nature. In such complexes, the neurosecretory material is stained with chromhematoxylin while the secretion of the glandular cells exhibits acidophilic properties (14, 19, 108, 114, 116, 229). The neurosecretory material is finely granular and easily differentiated from the mitochondria in fresh prepara-

FIG. 27. Neurosecretory fibers from the crossing nervus corporis cardiaci of *Leucophaea maderae*. Chromhematoxylin-phloxin. × 392. [From Scharrer & Scharrer (289).]

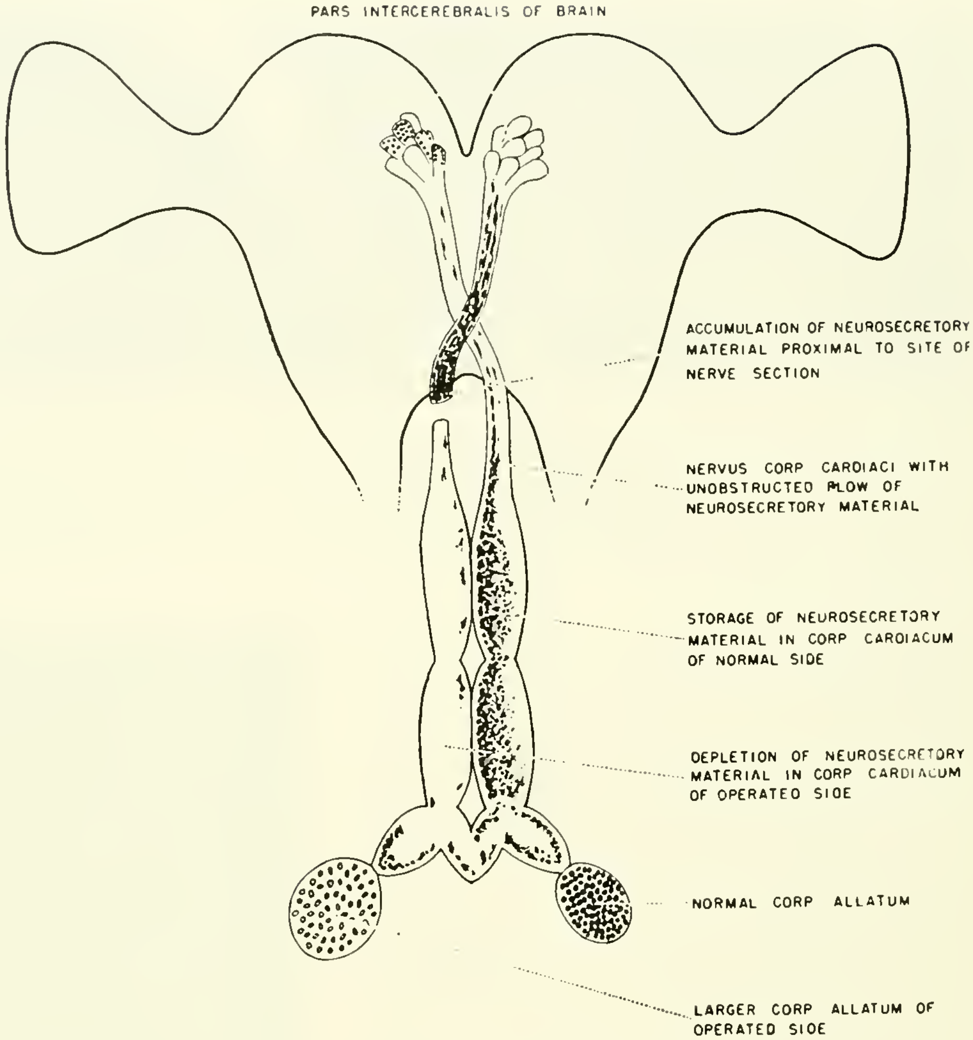


FIG. 28. Diagram of the dorsal aspect of the intercerebralis-cardiacum-allatum system of *Leucophaea maderae*. On the *left side* the nervus corporis cardiaci is severed with the result that neurosecretory material is increased proximal to and is depleted distal to the site of nerve section. On the *operated side* the corpus cardiacum is decreased, the corpus allatum increased in size. [From Scharrer (278).]

tions on the basis of its refractive properties. Neurosecretory cells frequently exhibit considerable vacuolation in certain functional stages of activity (fig. 26). Neurosecretory pathways are particularly apparent in many forms (fig. 27), with their direction of transport being readily demonstrated by transection and even ligation of the tract, as shown in figure 28 (278, 322, 337). Bead-like accumulations of neurosecretory material have been observed along the axons of living nerve fibers. As in the case of vertebrates, the neurosecretory elements in invertebrates possess conductional capacity [Milburn, quoted by Bliss (49)] the physiological significance of which is unknown. By and large, the morphological as well as physiological and biochemical (260) aspects of neurosecretion have been investigated more intensively in the invertebrate kingdom. However, no single case has received the attention paid to the supraoptico-hypophysis system. Two basic principles of hypothalamic-pituitary relationship have been well established for invertebrates; *a*) the neurosecretory material is carried over neuronal pathways to a depot or reservoir from which it is released into the blood stream or the peripheral tissues according to the needs of the organism and *b*) the neurosecretory material delivered to the glands of internal secretion

influences and regulates the secretory activity of these organs.

Neurosecretory Activity in Various Classes of Invertebrates

VERMES. The annelids represent the first class of invertebrates to exhibit significant patterns of neurosecretory activity. Neurosecretory activity has not been observed in the coelenterates and has not been established with certainty in the flatworms. In the free and sessile polychaete annelids, neurosecretory elements exhibiting possible cyclic secretory activity have been found in the cerebral ganglion and in the ventral nerve cord (13, 274). Although there are no notable sex differences, the neurosecretory phenomenon in nereids does undergo changes correlated with reproductive activity (93, 276). In *Lumbricus*, neurosecretory cells have been observed in the cerebral and esophageal as well as in both anterior gastric ganglia, with neurosecretory material being transported as far as the fourth gastric ganglion (60, 154, 158, 277). In *Lumbricus* also there appear to be functional relationships between the neurosecretory elements and the reproductive apparatus (alpha cells) as well as to regenerative phenomena (beta cells) (175, 176). In the group of sipunculids, neurosecretory elements are found in the brain of *Fasculosoma vulgare*, extracts of which act to slow down the contractions of the nephridia (185, 313). In five species of Onychophora, neurosecretory activity has been observed in the cerebral ganglion as well as in the ventral nerve cord. In these forms, the secretory activity may be cyclic, but there is no notable evidence of transport of secretory material or participation of the nucleus in the secretory activity of the cell (113).

ECHINODERMATA. Neurosecretory activity has not been observed in this phylum of invertebrates.

MOLLUSCA. In 25 species of prosobranchs which have been investigated, neurosecretory elements are exceedingly variable with the supraintestinal and pleural ganglia exhibiting evidence of secretory activity most frequently. In 35 species of opisthobranchs, evidence of neurosecretory activity has been observed most consistently in the cerebral ganglion. In both classes of animals, the seasonal variation in neurosecretory activity appears to be related to the maturation of gonadocytes (107, 110, 111, 275, 277). A uniformity has been found in the lamellibranchs where the cerebral and visceral ganglia have consistently exhibited neurosecretory activity and the pedal ganglia none (119). The secretory phenomena of the peduncular and epistellar glands of the cephalopods is not considered authentic neurosecretion (119).

ARTHROPODS. The morphological aspects of neurosecretion have been most extensively investigated in this phylum of invertebrates, and accordingly the greatest insight into its functional role has been gained here. Studies on the decapod crabs have shown the neurosecretory cells to be present in the brain and especially in Hanström's organ of the eye stalk, the axons of which join in a common path and end in the sinus gland. Historically these cells were the first neurosecretory elements described in invertebrates (146). In the sinus gland, the enlarged terminations of these nerve fibers assume a relationship to a central blood cavity (50–52, 64, 65, 147, 248). These neurons contain granular inclusions which may coalesce to form larger complexes which are visible in unstained preparations and which can be stained specifically with chromhematoxylin. Numerous mitochondria are present in these cells and are readily differentiated from the neurosecretory material (249). A minimum of three different types of secretory neurons have been distinguished. The sinus gland is considered as a reservoir for the several kinds of neurosecretory material delivered to it from these cells. Removal of the entire eye stalk leads to increased respiration, a fall in respiratory quotient and water intake. These changes do not occur when the sinus gland alone is removed leaving intact and functional those neurosecretory cells in the brain producing the effective hormones. After transection of the tract from the x-organ to the sinus gland, there occurs initially a depletion of the neurosecretory material at the site of the cut, followed later by a complete regeneration of the sinus gland (47, 48, 52, 99, 247). Along with the regeneration of the sinus gland, there is said to be a complete restitution of its functional activity (52). At least three chromatophoric hormones and other substances exerting an influence on the pigments of the eye are said to be formed in the ganglia optica in addition to those substances which regulate molting, and calcium and water metabolism. Bliss (49) has investigated the role of this system in growth and regeneration as well as the influence thereon of light, temperature and other conditions. The tritocerebral commissure constitutes a second center containing neurosecretory elements extracts of which influence the chromatophoric hormones (182, 185). In certain diplopods, members of the class Myriapoda, specific axons demonstrable with chromhematoxylin are pres-

ent in the protocerebral region (116). Fibers from these neurons pass to a gland the cells of which contain an acidophilic secretory material. No neurosecretory elements are present in the Julidae (287). Fibers from neurosecretory cells in the dorsal aspect of the protocerebrum of chilopods terminate among the cells of the 'glande cerebrale' and influence the formation of an acidophilic secretory material (120).

INSECTS. Weyer (336) was the first to demonstrate morphological evidence of neurosecretion in insects (bee), while Kopec (186) was the first to demonstrate the hormonal nature of extracts of insect brains. A very large number of species in the rich insect group has been investigated at least in preliminary fashion with respect to neurosecretion. Uniformly, neurosecretory elements are found in several segments of the protocerebrum, especially in the pars intercerebralis. The subesophageal ganglion is somewhat less consistent in this respect. The axons of the pars intercerebralis unite to form a neurosecretory pathway leading to the paired corpora allata, the corpora cardiaca and a series of glands named according to the species investigated, the pericardial gland, the prothorax gland and the peritracheal gland. Although the relationship between these glands and the neurosecretory elements of the brain is not completely elucidated, they do appear to be influenced by neurosecretory control in the formation of hormones concerned with the pupal stages. Cells of the glandular corpora cardiaca filled with a rich acidophilic secretion are surrounded by axons containing much neurosecretory material (18). Extracts of the corpora cardiaca affect the musculature, water content (7), malpighian vessels and activity of the heart (331, 337), as well as pigment activity (91, 92). Neurosecretory control of the corpora allata appears to extend to fat metabolism and egg production also. In the silk moth, neurosecretory cells have been demonstrated in various segments of the protocerebrum as well as in the frontal and subesophageal ganglia. In this species also, neurosecretory pathways from the pars intercerebralis terminate in the corpora allata and the corpora cardiaca with discrete secretory phases correlating with the formation of the pupal stages (159). In the adult, egg laying appears to be dependent upon neurosecretory activity. The neurosecretory elements in the subesophageal organ do not appear to exhibit any cyclic activity or secretory phases (15, 57–59, 112). The prothorax gland is believed to be the site of formation of those hormones concerned with the pupal stages (106, 337). In *Phasmida*, changes in coloration may be influenced by neurosecretory pathways from the trito- and deuterocerebrum. Neurosecretory activity from the pars intercerebralis appears firmly associated with growth and molting and to a lesser extent with egg formation and egg laying (90–92). In the orders Diptera and Hymenoptera, neurosecretory pathways are described from the pars intercerebralis to the corpora cardiaca and corpora allata (325). In Calliphora, Thomsen has succeeded in blocking the flow of neurosecretory material and demonstrating its direction of flow from the pars intercerebralis to the corpora cardiaca and allata (322, 323). Observation of living fibers from this tract indicates that they contain a clear, characteristic bead-like substance (324). Evidence of neurosecretory activity has been demonstrated in the arachnoids (114, 115, 118), in the pycnogonida (270) and in the tunicates (27, 62, 80, 250).

CONCLUSION

At the present time the information which would be required to build up a general concept of the significance of neurosecretory phenomena is still scanty. Nevertheless, there can be no doubt that neurosecretion plays an important part in the regulation of life processes in both vertebrates and invertebrates. Two facts have emerged as particularly striking: *a*) in these two groups of animals neurosecretory processes are concerned with similar functions, such as water and mineral metabolism and reproduction; and *b*) neurosecretory substances are not species-specific, in fact they are not even class-specific (318).

Neurosecretory processes must be involved in various biological processes as well as acting as mediators between the nervous and endocrine systems. Of particular interest is the as yet poorly understood relation between the capacity of certain neurons both to conduct impulses and to carry on neurosecretion. That they can make possible hormone transport to definite parts of the body must have a special significance. These considerations make it not unlikely that the neurosecretory processes are phylogenetically quite old (152, 341).

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Posture and locomotion

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CHAPTER CONTENTS

POSTURE

SIR CHARLES SHERRINGTON, more than any other investigator, has contributed to our understanding of the key neuromuscular relationships underlying posture. In his words, "Standing is a large and composite postural reflex and in its execution a fundamental element is the contraction of the antigravity muscles counteracting the superincumbent weight that would otherwise flex the joints and cause the body to sink to the ground" (170).

The experiments which led Sherrington and his co-workers to this viewpoint were principally their demonstration of myotatic reflexes in decerebrate animals (43). Resection of those portions of the brain anterior to an intercollicular plane releases the facilitatory activity of the lower brain stem from descending inhibitory influences and results in a state of exaggerated contraction of antigravity muscles (237), a 'caricature of normal posture.' Denervation of skin, other muscles and finally appropriate dorsal roots reveals that the tonic contraction is chiefly dependent upon afferent messages from the muscle itself (71, 170). Furthermore, the muscle exhibits plasticity for, when forced to lengthen, it is increasingly resistant (because of the stretch reflex) up to some critical point, whereupon with the suddenness of the closing of a clasp knife it gives way (by means of the lengthening reaction). If, after a pause, further lengthening is attempted, the same initial resistance and eventual yielding are felt, so that successive lengthenings with renewed assumption of tension at the new length may be repeated every few degrees over the total range of excursion of the joint. Finally, to complete the picture of plasticity, when the muscle is now allowed to shorten, each new length is marked by a new and specific level of contractural tone (through the shortening reaction).

Sherrington grouped these lengthening and shortening reactions, and the stretch reflex, together with the phasic knee jerk and clonus phenomena, under the term 'myotatic reflexes' (170). A limb deprived of myotatic reaction by severance of its dorsal roots is incapable of postural contraction, although neuromuscular power may be demonstrably adequate to bear the body's weight during elicitation of nonmyotatic reflexes [e.g. the crossed extension reflex (43)]. However, intact segmental reflex arcs are not all that is required for effective standing. Myotatic reflexes in a spinal animal are much less impressive than in the decerebrate preparation, and even months after cord transection the hindquarters of a dog collapse during standing. Needless to say, the monkey, cat or dog with combined dorsal root and spinal cord section manifests complete flaccid paralysis (263, 264).

It is evident that supraspinal contributions are essential to effective postural contraction. These, together with the afferent and efferent aspects of posture, are to be considered in the following sections. Only a few generalities concerning the many contributions of central nervous structures to tonic contraction can be mentioned, the reader being referred to other chapters for further details.

AFFERENTS CONCERNED IN POSTURE

Sensory fibers, if they are to figure prominently in reflex posture, should have these qualifications: *a)* the adequate stimulus for the sensory ending should be that of gravity acting upon the body parts, *b)* the afferent discharge should be sustained under this stimulus and *c)* central connections of the afferent fiber should result in facilitation of motor pools of antigravity muscles. Sensory modalities will be discussed with these features in mind.

Afferents from Muscle

The principal afferents in muscle are the annulospiral and flower-spray endings of muscle spindles, and the tendon organs of Golgi [cf. reviews by Granit (94) and Barker (9)].

MUSCLE SPINDLES. True spindle organs of muscle are those intramuscular receptors having specific contractile fibers as well as sensory wrappings; they are found widely in skeletal muscles of crustaceans, amphibians, reptiles, birds and mammals. Almost all skeletal muscles may contain them, with the exception of facial, internal ear and infrahyoid muscles; extraocular (42) and glossal (40) muscles, in which they were earlier thought to be lacking, now are known to contain spindles in some animals, including man. Obviously, the function of these organs is not exclusively postural.

A spindle from cat gastrocnemius muscle, to take a typical example, consists of a fusiform sheath of connective tissue which loosely encloses 3 to 10 small muscle fibers. Each of these intrafusal fibers has two tapering, striated motor poles and a central, unstriated region containing a dozen or more nuclei in a nuclear bag. Presumably, the nuclear bag is not contractile, nor perhaps even conductile, which may account for the presence of one or more motor endplates on each motor pole. These motor fibers are small enough (the mode being at 5 to 6 μ) to contribute to the gamma wave of a neurogram produced by stimulation of a mixed nerve at a distance from a pickup electrode. Extrafusal fibers of the gross muscle are supplied with alpha-sized motoneurons (with a mode of 16 μ).

Direct evidence of electromyographic potentials from intrafusal fibers in the very thin tenuissimus muscle of the cat (154), and the indirect evidence of accelerated afferent discharge during selective stimulation of gamma efferent fibers (165) indicate that intrafusal fibers are contractile. Their small size and rarity of occurrence in any cross-section of a muscle belly (1 to 10 spindles in cat medial gastrocnemius) have rendered futile efforts to detect contributions to muscle tension by intrafusal fibers (94, 154, 165, 210). Apparently gamma motoneurons innervate only intrafusal fibers, for selective stimulation of these efferents does not directly increase postural tone (210). The relation to postural tone of the sensory circuit through spindles will be mentioned in a later section.

Sensory endings of two types are wrapped about the individual intrafusal fibers: a primary ending encircling in annulospiral fashion the nuclear bag, and a secondary ending, or flower-spray terminal, one of which generally clasps proximal portions (myotube regions) of each motor pole. Although easily distinguishable upon the basis of axonal conduction rates, the responses of the two types of spindle endings under various stimuli are so similar that positive identification from behavior alone is not always possible. However, by several indices, such as the behavior during twitches and irregularity of discharge, nuclear bag endings seem to be more phasic in reaction (59). The minimal tension of the muscle at which

firing is continuous is also less for nuclear bag endings than myotube terminals (125). At low tensions this difference should permit pure annulospiral reflex effects unmixed with those of flower-spray or tendon organs, although this margin seems insufficient to provide full postural support without entry of flower-spray activity.

The salient features of the behavior of spindles as related to posture are these (94): *a)* passive stretching of the gross muscle increases the rate of repetitive firing, the frequency being roughly proportional to the muscle lengthening; *b)* adaptation is very slow—that is, upon stretch of the muscle to a new length the afferent discharge after a phase of rapid firing assumes within seconds a new level which is essentially constant over a period of hours; *c)* contraction of the gross muscle causes a decrease or cessation of spindle firing. The latter is most characteristically seen during a twitch induced by single-shock stimulation of a muscle nerve wherein a pause in the afferent discharge occurs with the rise in tension, followed by a spate of firing during the decline of the twitch. The pause is especially pronounced when the muscle is allowed to shorten. These facts suggest that spindles lie in parallel with the large muscle fibers, as is readily verifiable histologically; and *d)* contraction of an intrafusal fiber accelerates the discharge from its associated endings. If gamma firing increases concurrently with contraction of the gross muscle, shortening of the intrafusal fibers may overcompensate for that of the matching span of extrafusal fibers and an actual enhancement of discharge may ensue.

Since discharge from spindles is modified by both extrinsic lengthening of the muscle and the intrinsic contractile status of intrafusal fibers, these organs do not act as specific indicators of muscle tension or length (57). Their discharge, in a general way, varies inversely as the ratio of the length of the contractile pole of the intrafusal fiber to the length of extrafusal fiber lying opposite the entire spindle; that is, it is a measure of the relative lengths of intra- and extrafusal fibers. The organization of reflex tone is presumably based upon such information.

TENDON ORGANS. The encapsulated tendon organs of Golgi are found in ligaments (4, 22), or at myotendinous junctions where they are in series, as it were, with the line of stress and can serve to register tension. Thresholds and adaptation rates are decidedly higher than those of spindles and, except for brief discharges under sharp changes of tension, firing appears only with moderate tension. Efferent innervation for tendon organs is unknown.

CENTRAL EFFECTS OF MUSCLE AFFERENTS. The central effects of muscle afferents upon decerebrate rigidity, tendon jerks, monosynaptic reflexes or other motor phenomena are known from experiments in which the afferents have been selectively stimulated by: *a)* cutting of the tendons and other procedures directed at the muscle (41, 73, 170, 195, 201); *b)* chemical stimulation of the endings (56); *c)* differential stimulation of various size modalities of afferent fibers from muscle (25, 161, 177); and *d)* alterations of the length and contractile state of the muscle (93, 115, 176). Additionally, there are supporting data on the physiological role of muscle afferents which are based upon *e)* histological observation of central terminations of afferent fibers (254); and *f)* detection of evoked potentials within the spinal cord (39). Although some question has been raised as to whether results obtained upon phasic indices of motor function can be freely translated to tonic states (186), the above evidence agrees well in ascribing functions to the three classes of endings in extensor muscles as follows: *a)* the discharge from tendon organs is inhibitory to homonymous and synergistic muscles; *b)* annulospiral afferents on the other hand facilitate extensor contractions, while *c)* flower-spray endings probably inhibit the homonymous extensor (25, 115, 116, 124, 161, 177). In addition, each ending exerts reciprocal effects on the opposing muscles.

Annulospiral endings are thus the mainsprings behind stretch reflexes and postural tone. However, only at very low tensions is the overall central effect of the discharge from de-efferented extensor muscle facilitatory to itself, at least in cat gastrocnemius (93). At most imposed tensions greater than 5 or 10 per cent of the contractile power of the muscle, that is, even at tensions unlikely to arouse tendon organs importantly, the net effect upon monosynaptic testing is inhibitory. The imbalance toward inhibition is modest, as moderate alteration of the experimental condition of the animal (such as cooling) causes facilitation (115).

OTHER AFFERENTS IN MUSCLES. Fiber diameter spectra of nerves to chronically de-efferented muscle reveal that there are, besides group I (annulospiral and tendon organ afferents) and group II (flower-spray afferents), other myelinated and unmyelinated fibers with diameters less than 6 μ. Identification of specific sensory terminals with these small fibers has not been

well demonstrated, nor are the physiologically adequate stimuli for these endings known. Their stimulation probably leads to general flexor withdrawals (25, 174) and pain responses (18, 210), but contractions restricted to the homonymous muscle have also been noted (18, 210).

Afferents from Joints

Sensory endings in and about joints may be classified as tendon organs, Ruffini endings, Pacinian corpuscles and an additional heterogeneous category of simpler endings (23, 77, 78, 248).

PACINIAN BODIES. Corpuscles of Pacini are found in mesenteries, interosseous membranes, occasionally in fascial planes of muscle and, importantly from the present standpoint, in clusters located deep to flexor tendons of the digits (107). It is noteworthy that neither in the latter location (107) nor about the knee joints of the cat (23, 38, 78, 248) or mouse (77) do Pacinian bodies bear a principal relation to joints; rather they lie in locations favoring deep pressure as an adequate stimulus. The application of a rod or bristle directly to an isolated corpuscle elicits a discharge which rapidly decrements (22, 105, 107) and cannot be made to continue longer than 5 sec. despite continued pressure and deformation (107). These organs, therefore, are suited to signal quick changes in pressure (248) such as occur in the acute strains imposed on plantar surfaces of the digits upon initial contact with the ground as in the extensor thrust reaction. It is not certainly known that Pacinian bodies participate in muscle reflexes and, indeed, in mesenteric locations it has been claimed that they mediate vascular reflexes (76).

RUFFINI ENDINGS. In monitoring single units from joint nerves (such as in the knee of the cat), the most prevalent pattern of discharge is one in which firing occurs over a limited extent of the flexion range and a maximum frequency is found at some optimal position (23, 38, 107, 248). Flexion-extension or rotation of the joint causes the unit first to respond with momentary overfiring or underfiring and then to settle to a new frequency which is characteristic of that position (4, 23). Essentially, the same rate is attained whether the final position is approached either from a position of greater flexion or of extension (38). This afferent pattern has been identified fairly definitely with the endings of Ruffini (22, 23, 248). These are strewn widely among the multidirectional strands of the fibrous capsule and ligaments, thus accounting for the variation in ranges and optima for firing of individual receptors and providing, theoretically, a series of permutations of receptor responses by which the central nervous system may judge the position of the joint. At no position of the joint are all endings silent (23, 38).

TENDON ORGANS. Sensory endings similar to the organs of Golgi in tendons are present in cruciate, patellar and collateral ligaments but not within the capsule proper (248). For this reason, unlike Ruffini endings, the tendon organs of joints are relatively unaffected by contractions of muscles which insert in the vicinity of joints (248) and could conceivably serve as an even more reliable indicator of joint position. The discharge from tendon organs of joints, like that from muscles, adapts slowly.

CENTRAL EFFECTS OF JOINT RECEPTORS. Stimulation of articular nerves in the spinal or decapitate cat elicits polysynaptic discharges in the ventral roots, an inhibition of extensor monosynaptic responses and a facilitation of flexor ones (15, 79). With stronger stimuli, signs of pain with flexion of all limbs and the trunk appear (79, 81). Nevertheless, in the decerebrate preparation, flexor responses are not invariable (79, 248) and perhaps, if more discriminate stimulation were employed, flexor and extensor effects would be found to depend upon the position and nature of the ending. Certainly receptors at some joints (such as the cervical intervertebral) may facilitate either flexor or extensor effects, depending on the direction of movement. Joint receptors, by reason of their strategic locations and the tonicity of their discharge, might be suspected of influencing postural contractions, and such a role of cervical receptors is well known as underlying the attitudinal reflexes. The entire role may be a complicated one as joint afferents project to the somatosensory cortical areas (80, 248) as well as to the reticular formation (200).

Cutaneous Receptors

In general, skin receptors are unsuited to the task of mediating postural contractions by reason of their phasic discharge (69, 106, 108, 192) and flexor central effects (43); and, indeed, decerebrate standing can still be obtained though the skin be removed from the entire preparation (241). However, the positive supporting or 'magnet' reaction is elicitable in the decerebrate animal upon barest contact with the

foot pads where the afferents are presumably cutaneous (19) and of large caliber (111). Slowly-adapting mechanoreceptors in the distribution of the sural nerve have been described in the frog (180) and rabbit (69). This is especially interesting as stretch of the skin over extensor surfaces causes contractions of the underlying muscle in cats (58, 109), dogs (111), bullfrogs (111) and sometimes in man (228), a pattern which fits in well with postural activity. This relation between extensor skin and muscle is not universal, as stimulation of the skin of the back of the labyrinthectomized decerebrate dog causes a collapse of extensor tone (239).

Other cutaneous receptors may possibly contribute to posture. Unmyelinated 'C' fibers, for example, may weakly facilitate extensor muscles (160) and under certain types of pressure (pinpoint) have unceasing discharges (285). Cold receptors satisfy the criterion of having a slow rate of adaptation (117, 286) and stimulation of cutaneous surfaces by cold may lead to extensor response (214, 238). Cooling of the sole causes, incidentally, a positive Romberg response in man [Heyd quoted by Harris (111)].

Enteroreceptors

When man changes from the horizontal to the erect position, widespread displacement of mesenteric and even retroperitoneal structures, including the kidneys (199), occurs and hollow viscera such as the bladder may experience considerable alterations in pressure (92). Pacinian bodies and other receptors, which presumably are affected by these changes, are abundant in the posterior body wall, while the bladder wall and other viscera contain slowly-adapting endings which are sensitive to pressure (128). Stimulation of visceral receptors and nerves, although usually favoring contraction of abdominal flexor and psoas muscles, may sometimes cause contraction of the vastocrureus or lead to progressive movements (198). In intact man the knee jerk is enhanced during strong visceral contractions (132), and in spastic man the close relation of visceral receptors to flexor and extensor spasms is notorious (215). The observation that chronic midbrain animals are sometimes incapable of standing except while defecating may have a similar explanation (143).

Final Comment

The criteria, cited earlier, which sensory endings should satisfy if they are to figure prominently in reflex posture, are met, so far as present knowledge goes, by the annulospiral endings of muscle spindles and perhaps by the Ruffini endings of joints. The overwhelming importance of muscular afferents, that is endings in the spindles, in contractions of tonic nature was demonstrated conclusively by Sherrington. However, as shall be seen, joint receptors have also been suspected of playing a prominent role in posture.

EFFERENT SIDE OF POSTURE

The final expression of postural integration is determined by the combinations of motor nuclei which are activated and by the pattern of motoneuron activation within the nuclei.

Patterns of Motor Nuclei Activation

The word 'posture', although defined variously by the orthopedic surgeon (202), kinesiologist (253), behavioral psychologist (87, 229) or physiologist (170), connotes in each usage active muscular resistance to the displacement of body parts by gravity. For the quadruped this means contraction by those derivatives of the primitive dorsal musculature which extend the limbs, arch the back and raise the head and tail (197, 239). However, abdominal muscles (244) and the anal sphincter (65, 139, 197), which are fundamentally flexors, also participate, as do the special muscles of mastication. In man even the levator palpebrae and facial muscles may be suspected of some form of antigravity tone. Contraction of flexors would appear to be preponderant in the arms of the monkey (217), wings of the pigeon (244) or hind legs of the frog (244), while in the arboreal sloth, the balance of postural integration is completely flexor so that the caricature of normal posture seen in the decerebrate sloth is one in which the animal is curled into a tight ball (24, 226). The one feature which consistently characterizes motor nuclei active in postural tone is their innervation of antigravity muscles.

The question arises whether in the intact animal the activity of antigravity motor nuclei is coupled with reciprocal inhibition of antagonist nuclei. Certainly in the anesthetized or decerebrate animal (19), flexor participation in the positive supporting reaction may be strong, but the fact that contractions often radiate to all muscle groups under extreme excitation (167, 228) makes inference from these exaggerated states to the normal one uncertain. Electro-

myographic monitoring of activity in opposing pairs of leg muscles in man indicates that the contractions are reciprocal (167).

Patterns of Motoneuron Activation

The participation of neuronal and muscular elements in postural contraction is imperfectly known despite innumerable observations beginning with those of Ranvier in 1874 (224). Much older work attempted to attribute tonic contraction to supplementary innervation of striated muscle by sympathetic or parasympathetic systems [for reviews see (118, 259)] or to gamma-sized motoneurons (110). These efforts have failed of convincing demonstration, and current thought holds that all skeletal muscular contraction in mammals is mediated by alpha motoneurons (146, 154, 259). Assuming for the present that all muscle fibers in a motor unit contract in response to a single axonal impulse, three possibilities exist by which a motor pool may maintain submaximal contraction of a muscle: *a*) all neurons may be in continual but submaximal action; *b*) all neurons of the pool may participate but only a few discharge at any one time; or *c*) selected motor units may be in continual action, the others remaining idle until recruited for phasic or stronger tonic contraction.

The fact that motor units are activated at higher rates as the strength of contraction increases is well known. It appears, though, that this mechanism may have limited application for, in moderate contraction of the muscle, this increase in rate is not large as compared with the minimum rate at which the unit fires (17). At any rate, most accounts of single unit electromyographic recording note the entry of new units as contractions are intensified.

The persistent idea that units engaged in tonic contraction are in rotational activity (7) first received wide attention following a review by Forbes (67) in which it was mentioned as a mere speculation. Evidence from electromyographic sampling of single units of muscles in sustained reflexes, decerebrate rigidity or voluntary contractions (1, 17, 121, 221, 225, 249, 272, 278), however, has not revealed such rotation. Active units, on the contrary, may fire continuously for over one-half hour in sustained (171) or repeated contractions (88). Presumably, such units do not fatigue because the low rates of motoneuron discharge (1, 17, 221) are below the frequencies required for tetanic fusion of single units (90). Even extraocular muscles, to which motoneurons may discharge at rates up to 170 per sec., are not maximally taxed, for fusion thresholds are correspondingly increased to 350 per sec. (225). Although rotation in the above sense is unsubstantiated, fluctuations in activity between motor pools or segments of the pool of a single muscle might be expected to result from the kaleidoscopic adjustments of balance made by the animal's body. These waverings are seen impressively on cephalograms taken during Romberg testing in man (113). They could, through localized stresses within a muscle, cause myotatic contractions of single heads (170) or even minute slips of the muscle (37, 170). The alternative to equipotentiality among units in a motor pool, and the implied rotation during submaximal contraction, is differential sensitivity among the motoneurons. The amphibian provides a complete illustration of this, for tonic contraction, attaining perhaps 15 per cent of the available muscle strength, is mediated by a distinct class of ventral root fibers of small caliber which lead to special small muscle fibers (153, 155, 156, 256). The latter have slow, sustained and nonpropagated contractions, whereas the larger muscle fibers, which are innervated by neurons of greater size, contract only phasically (153). The small nerve system has a lower threshold to cutaneous stimulation than the large one and is thought to be the instrument of postural tone (146, 155). Crustacea also have a dual contractile mechanism (152), sometimes with the additional complication of inhibiting neurons (279).

In mammals little is known concerning the relations of the motoneuron to red and white, bright and dark, field and fibrillar or other descriptive types of muscle fibers (21, 150, 282). Even the functional inference that red and white muscle types correlate with speeds of contraction is questioned (46), although the generalization that red muscle is concerned primarily with sustained contraction (112, 207) continues to receive support. Several investigators, for example, have noted that the soleus, a relatively red muscle even in man (268), is more active in standing than other heads of the triceps surae (1, 47, 70, 133, 144, 206). Units in deeper portions of muscles, where lie muscular heads (46) or strata (48, 91) of redder fibers, often have low thresholds in tonic contraction (138), tendon reflexes (47) or in the spastic activity in paraplegia (47). Even in the anterior tibial muscle, a physiological flexor, red portions have a lower threshold and longer after-discharge to elicitation of flexor reflexes or stimulation of the motor cortex than paler and faster-contracting superficial layers (91). Similar elicitation of flexor reflexes, however, seems in the rabbit to cause the pale semimembranosus to

contract more readily than the red semitendinosus (112).

In voluntary contraction of a muscle, activity is consistently aroused in some single units earlier than in others (47, 50, 127, 157, 234, 249) Also, units activated in willed 'primary' movements are not the same ones that first appear when the muscle is acting in accessory postural fixation (47, 234). Although interpretation of disparity in the size of potentials as picked up by unifocal electrodes is difficult (47, 131), it is suggestive that the units activated in fixation (47) and those appearing only secondarily on voluntary contraction (157, 208) have relatively large action potentials. This is somewhat paradoxical, for units with high thresholds in voluntary contractions are late to respond to galvanic stimulation of motor nerves which indicates that their axons are small (157). In accord with the latter finding, fragmentary histological evidence indicates that motoneurons to red, or tonic, muscles are smaller than those to their immediate companions of paler composition, e.g. the soleus versus the gastrocnemius (46, 54, 245, 256); this is, perhaps, also true for the medial versus the lateral head of triceps brachii (61), and the semitendinosus as compared with the semimembranosus (61). It can only be said at present that relationships between the axon size of a motor unit and its evoked EMG potential are not well known (208).

Tokizane and other Japanese workers (70, 138, 139, 141, 260), in studies on the motor units of human muscles, have come to recognize a 'kinetic' type of uneven discharge and a more uniformly firing 'tonic' type upon the basis of irregularity of spike-to-spike intervals in the discharge of single units. It is inferred that these units mediate phasic and tonic contractions, respectively, and in accord with this the relative number of kinetic and tonic units varies with the functional nature of the muscle. The gastrocnemius, for example, has more kinetic units than the soleus (70). Similarly, the abductor pollicis muscle is largely kinetic (138), while the sphincter ani is tonic (139). Perhaps related to this characterization is the observation that units which are preferentially activated in 'primary' movements tend to fire in asynchronous showers, whereas those activated in contractions serving purposes of fixation have a periodic discharge (47). A claim has been made that two types of electromyographic units in man and other mammals may be separated by curarization or by hypnosis (230).

Recently, attention has been directed to the motoneurons themselves for evidence of two kinds of units. Some gastrocnemius motoneurons, for example, may consistently be induced to fire at lesser degrees of stretch of the homonymous muscle, or intensity of electrical stimulation of the muscle nerve, than other units (3). Granit and his co-workers have separated the units in the motor pool of the triceps surae muscle (i.e. both red and white muscle) into phasic and tonic units, according to the duration of firing in response to single shock stimulation of the muscle nerve after a preceding period of tetanic stimulation (96). Also, Eccles and his co-workers, through the use of intracellular electrodes, have distinguished tonic and phasic motoneurons in the motor pools of a variety of muscle complexes (53) They characterize the tonic units as exhibiting long-lasting after-hyperpolarization, more general accessibility to monosynaptic activation from afferents of synergistic muscles and slower conduction rates in their axons. Separation of units into tonic and phasic classes is not sharp, however (53), and wide variation in responsiveness of units is found if rigorous steps are taken to ensure revelation of all units capable of firing monosynaptically upon stimulation of components of the triceps muscle nerve (179). Furthermore, since firing indices of individual units may be shifted drastically by alteration in the background level of facilitation, it is difficult to decide whether variation in firing capacity is truly bimodal or not (179). Certainly curves relating the height of monosynaptic response to stimulus strength do not show the bimodality (175) which would be required if there were two classes of neurons of greatly differing thresholds to monosynaptic testing.

Conceivably, even though motoneurons of a given motor pool are all of the same type, muscle fibers of dissimilar nature might be differentially stimulated through partial blocking of the passage of impulses onto some branches of the axon, such as the thin 'accessory fibers', or across some myoneural junctions. Such exception to the principle of all-or-none contraction of the motor unit has been adduced to account for the graded augmentations of muscle action potentials produced by stretch or a preceding period of indirect stimulation of the muscle [see review by Hodes (120)]. In chickens, for example, it is claimed that one quarter of the gastrocnemius fibers, which respond after a conditioning shock or tetanic stimulation of the motor nerve, do not contract following an isolated shock to the nerve (29). Normal mammalian muscle may also exhibit augmentation of potential during a series of supramaximal indirect stimuli (208), but generally the phenomenon is

seen only under partial curarization (169), in neuromuscular disease (120, 278) or in fatigue (222). Should multiple innervation of single muscle fibers of the type shown for the frog (126, 137), rat (131) and cat (126) prove widespread, it may become necessary to re-examine the concept of overall contraction of individual muscle fibers as well as that of motor units.

Postural Maintenance in Man

The importance of tonic reflex contraction in the postural maintenance of man has been questioned by several investigators who, using needle electrodes, found essential electromyographic silence in the gastrocnemius, soleus and tibialis anterior muscles during 'easy standing' (11, 36, 121, 134, 144, 235, 272). Others deny these findings (47, 133, 206, 209); but the difference in opinions is in part semantic, for all observers agree that at the extremes of postural sway corrective contractions take place. The importance of training in obtaining adequate relaxation should also be emphasized (267).

Direction of interest to the play of muscles about the ankle only partly reveals the role played by active contractions in correcting imbalances at this joint, for compensations can result as well from shifts in the center of gravity produced by hip or trunk movements. The lower reflex threshold and greater prominence of tonic contractions (43, 217), and greater sensory discrimination at proximal joints (89) as compared to distal ones, point to the importance of proximal joints in posture. Pigeons, to use another biped as an extreme example, roost fully as effectively upon a leg in which the foot and ankle are denervated as upon the sound leg (34). In man observations upon deeper muscles of the hip during standing are lacking, but the related sacrospinalis muscle may be silent (64, 221) or nearly so (36), as is also the rectus abdominis (63, 140). More important, however, considering that the line of gravity falls posterior to the hip joint (62), are indications that activity is continuous in the oblique abdominal muscles (63, 255).

Reaction against Sherringtonian views of postural tone has led Clemmesen of the Danish group of muscle physiologists to declare that "we must reckon with the passive elastic tensions and forces in the muscles, and (the fact) that this concept is much more correct than the now discarded concept of muscle tone" (36). He and others (2, 121, 235, 267) point out that stretching of muscles in normal man, including those about the ankle (272), leads only to reflex contractions at rapid rates or considerable lengths of stretch. Muscles in the stub of a kineplastic amputation, for example, may be lengthened 50 per cent without eliciting detectable electrical changes (221). Kelton (144) argues that postural contraction may be more closely geared to joint than muscle receptors since activity in the soleus muscle of a standing man may be initiated by a rate and degree of angular deflection which was incapable of eliciting a stretch reflex in the resting muscle. In animals with greater extensor tone, including those decerebrate, on the other hand, the sensitivity of stretch reflexes may be exquisite, the threshold for the gastrocnemius being 50 μ (170), and for the supraspinatus 8 μ (48) of lengthening.

The ability of man to stand with little expenditure of neuromuscular energy derives from the elasticity of ligaments and muscles, the mechanical features of some joints and the fair compensation with which the centers of gravity of body segments are superimposed (2). The role of elastic nuchal ligaments in suspending the head of a herbivore is well known; but similar postural functions in man of the ligamenta nuchae and flava, the twisted iliofemoral ligaments and crossed ligaments of the knee are insufficiently appreciated (2). Elasticity of the muscle and its sheath is not an inconsiderable factor (34, 135, 267), and even in Sherrington's decerebrate animals, denervated muscle exhibited as much as 10 per cent of the tension developed by the innervated and highly hypertonic muscle when stretched to some lengths (43). In man the elastic tension of the calf muscles, at the usual angulation (88°) of the ankle, has been measured and found to be essentially equal to the gravitational forces tending to tip the body forward (134). The plastic qualities of muscle, on the other hand, are probably of less importance in postural maintenance than they are in locomotion where they become a major factor in limiting the speed of movement (75).

Experimental observation has shown that an aim of postural integration in man is to keep the center of gravity of the body directly (within 7 per cent) over the center of the basis of support (10, 113). Contrary to statements based upon a misunderstanding of the meaning of 'Normalstellung', as used by the original workers in this field [evaluated by Brunnstrom (33) and Hirt *et al.* (119)] the line of gravity of the average individual does not pass successively through the axes of the major joints. Rather, it passes posterior to the interacetabular line, anterior to the knee joints, and several centimeters in front of the ankle joint to

fall finally midway between calcaneal and metatarsal points of support (2, 33, 202, 253). Active muscle support is largely avoided at these levels, however, by mechanical arrangements (62, 181). At the hip, for example, the iliofemoral ligaments together with elastic forces of the muscles may in some individuals be adequate to prevent overextension in standing (2, 135). The pull of these ligaments in turn holds the femora in medial rotation, thus preventing the unlocking rotation at the knee joint which is necessary for flexion (2); that the quadriceps tendon is relaxed in standing is easily verified (2). At the tibio-astragalic articulation, the body is prevented from falling forward when the foot is abducted by the fact that the planes of flexion of this joint in the two feet form an angle of 60° open to the front. Teetering forward then requires that force in part be directed along the axes of a hinge joint rather than entirely in its plane of flexion (181).

To summarize, it is apparent that the function of the neuromuscular system in standing man is less one of steady antigravity contraction than one of intermittent correction of balance. On the other hand, consideration only of evidence from subjects 'standing at ease' perhaps overemphasizes the importance of passive balance, for people assume a symmetrical position only 20 per cent of the time spent in casual standing (250). Furthermore, man is unique since most other mammals, including prehistoric man and the great apes (202, 229), have standing postures characterized by partial flexion of limb joints with the corresponding requirement for tonal support.

CENTRAL ASPECTS OF POSTURE

Central Facilitation of Postural Reflexes

The function of the central nervous system in posture is, in essence, the translation of the variegated influx of afferent impulses into a steady and directed flow of efferent discharge. Segmental levels are basically capable of this integration. The dog, for example, several months after transection of the thoracic cord, can rise from a sitting to an erect position and stand for a time (193, 244), occasionally even on one hind leg (241). Similarly, spinal man can be made to support his body weight, if reflex-initiating pressure is maintained over the popliteal region (158). Yet postural performance in the spinal animal is incomplete. After minutes or a half hour of standing, the hind quarters of the spinal dog collapse, either gradually and without apparent stimulus or suddenly in response to some minor incident favoring a flexor response (244). Moreover, behavior in such chronic animals hardly represents quantitatively the conditions in the intact animal because of the acquired sensitization of spinal centers (257). Acute spinal dogs or cats show no ability to stand, even when the level of central activity is raised by amphetamine administration (190). Reflexes in spinal animals are characteristically abrupt and unsustained (43).

The additional background activity necessary to bring potential postural patterns to successful expression arises from several sources: *a)* somatic sensory inflow from other spinal and brain-stem levels; *b)* special sensory inflow from vestibular organs; *c)* the nonspecific activity of the reticular formation; and *d)* those relatively discrete influences descending from the cortex, basal ganglia and other brain structures. A discussion of the latter important contributions to posture must be left to other chapters.

SPINAL AFFERENT INFLUENCES. Sensory inflow over a dorsal root affects activity not only at that specific segment but contributes also to that of distant levels. Thus, sensory impulses from receptors of cervical intervertebral joints do not have their sole or even prime effect at the immediate segmental level. The labyrinthectomized cat cannot hold his head up, for instance, although the head be placed initially in the position favoring extension (217). Rather, the influence of these receptors is stronger upon the forelegs and extends as far as the hind legs. Even somatic afferents in cranial nerves may influence spinal levels, for example, the associated movements of distant limbs which accompany clenching of the jaw of the hemiplegic patient (269). It is not surprising in view of these facts that the incidence and intensity of reflex activity increases with the length of the cord segment in a spinal animal (104, 214, 215), or the number of dorsal roots remaining in a partially deafferented preparation (100, 173).

VESTIBULAR INFLUENCES. A powerful influence upon segmental postural reflexes is the vestibular inflow. Although under some circumstances the labyrinths appear to impart greater intensity to all components of motor patterns (72, 145), the net effect of this quinquifid inflow (that from the two maculae and the three cristae) is one of unfatiguing facilitation of antigravity muscle activity, both at spinal (84, 85) and cranial (244) levels. Nevertheless, sensory in-

flow from vestibular organs (as distinguished from the influences of vestibular nuclei) is not indispensable for standing of decerebrate preparations (240, 241) nor of intact animals, including man (68).

RETICULAR INFLUENCES. Yet another type of influence upon postural reflexes derives from the reticular formation, a region discussed in detail in Chapter LII by French in this *Handbook*. This diffuse region, fed continuously by impulses from a variety of origins, including vestibular organs (85), muscles and joints (42, 200), exerts a steady influence upon segmental reflexes and tonic contractions (251). In part, these influences may be expected to have specific and organized effects upon the body musculature since portions of the cephalic reticular formation contain ill-defined centers for some of the righting reflexes (188). In concept, at least, other activity may be more formless, a force for general motor arousal. Destruction (of facilitatory portions) of the reticular formation leads, indeed, to akinesia and hypotonia along with heightened thresholds for general arousal (189). In a positive sense the effects of the brain stem upon posture may be seen by contrasting the behavior of the decapitate cat with that of the cat in which the brain stem is deprived of all neck, labyrinthine and descending influences [except, in part, the cerebellum (218)]. This preparation exhibits a posture of waxy flexibility in which forearms are partially flexed, while hind legs are held in moderate extension. Attempts to flex any of the extremities meet moderate resistance which progressively increases as the flexing is repeated, a behavior which perhaps represents an 'arousal' of motor performance by the reticular formation.

A kindred example of a nonspecific central influence upon posture is the Schiff-Sherrington effect. If in a decerebrate cat the cord is cooled or cut at the thoracic level, the posture of the forelimbs is tonically shifted toward extension; or if the lumbar intumescence is the site of sectioning, enhanced extensor reflexes may be seen in muscles of the hind leg innervated by the cephalic segment, such as the quadriceps (43, 232). This release is not readily explainable in terms of simple pleurisegmental reflexes for, although reflex effects between forelimbs and hind limbs are elicitable in both ascending and descending directions, a reverse Schiff-Sherrington effect is not generally described, although such an observation has been made in the frog (281). Furthermore, the release of extensor activity in the forelimbs is seen even when the posterior cord segment has been acutely or chronically deafferented (231). Thus, it appears that there is a separate type of activity arising *sui generis* at lumbar cord levels or through long return circuits from superior levels (231).

Circulating endocrine secretions affect general motor activity (12) which suggests that they may enter into facilitation of postural behavior also. Stimulation of the reticular formation through the direct action of epinephrine (45), for example, could provide such action. A central action of progesterone has been postulated to explain the decreased tonus and electromyographic activity in abdominal muscles during pregnancy (140, 255), or following the administration of this hormone (140, 142). This action would favor development of the compensatory lordosis of pregnancy.

Significance to Postural Tone of Motor Innervation of Spindles

Conceivably muscle receptors of purely passive nature 'in parallel' with contracting fibers could provide a mechanism for reflex posture, as may be the case in fish. Their afferent discharge, varying as the length of the muscle, could at one optimal length be exactly sufficient to resist reflexly the load imposed on the muscle by gravity. Lengthening would arouse increased discharge, a greater contraction and a return of the muscle toward the optimal length. Posture under such a mechanism would be singularly inflexible, for muscles would always seek the fixed position of repose.

The problem of resetting sensitivity of spindle receptors, to permit establishment of an inflow-outflow equilibrium at any length of the muscle, may be solved by making the discharge of the sensory wrappings dependent also on the pull of a special muscle fiber which through central innervation may be held in partial contraction or 'bias.' In frogs this innervation consists of thin branches of motor axons leading to extrafusal muscles (136), so that compensation occurs for the unloading and decreased firing of spindles in active shortening. Each combination of length and contractile force of the gross muscle is presumably linked with a specific rate of afferent discharge, and upon the equational constants of this relationship depends the fitness of the external circuit through the spindle for sustaining the contraction without additional aid.

Mammals have added flexibility to spindle function by dissociating totally the peripheral innervation of extra- and intrafusal muscle. In this new

freedom, coactivity or reciprocal activity between alpha and gamma motoneurons may and does occur. Usually in spontaneous cortically-induced or reflexly-elicited motor responses, the activity of both neurons increases together so that the afferent discharge from spindles rises rather than drops during contractions. Parallel inhibition, too, of both types of motoneurons is found (94, 123).

Alterations in activity of alpha and gamma motoneurons are not simultaneous, or rather, the threshold for gamma effects is lower than that for alpha effects (63, 146). Distention of the bladder of the spinal cat, for example, may readily lead to spindle activation preceding, or in the absence of, alpha activation (Abdullah, A. & E. Eldred, unpublished observations). Furthermore, firing of lumbosacral gamma fibers may persist despite bilateral multisegmental section of dorsal roots, under which conditions alpha activity, of course, is absent in the decerebrate cat (57). Amphibian and mammalian proprioceptive systems, thus, differ not only in the greater independence of action possible in mammals but in that this independence is exercised to afford gamma efferents a greater sensitivity to reflex and descending influences.

The above observations, together with the knowledge that gamma efferents are readily influenced from a variety of brain structures (55, 94), indicate that this efferent system does not merely serve to adjust locally afferent inflow to changes in muscle length but has wide functional significance. The prominence of gamma activation in decerebrate animals (57, 123) and the known dependence of the stretch reflex upon annulospiral afferents suggest that postural maintenance is a part of this function. The observation that the net effect of afferent discharge from passively stretched and de-efferented extensor muscle is largely inhibitory to homonymous alpha (115, 124) and gamma neurons (123; *cf.*, however, 146) makes it appear that some degree of intrafusal tone may be requisite for the very existence of a stretch reflex. Simultaneous stimulation of a number of isolated gamma efferents leading to a muscle does, in fact, result in facilitation of the monosynaptic reflex (124). And of course, in the decerebrate animal, which has vigorous gamma efferent activity, stretch of the muscle leads to sustained facilitation of homonymous motoneurons (3).

The gamma efferent system, although a major mechanism behind postural tone, is not necessarily the sole one, for alpha neurons are also directly accessible to postural influences (252, 265). The cat, for example, which has been chronically deafferented bilaterally in the cervical and thoracic segments, then terminally decerebrated and spinalized at a low thoracic level, still demonstrates labyrinthine effects upon the forelimbs (219). Also, tonic contractions in deafferented limbs may be produced and coactivation of alpha and gamma neurons disturbed by alterations of cerebellar function (98).

Nor is it implied that tonic contraction is the sole concern of the mammalian gamma efferent system. Many considerations point to a close tie with phasic motility; the presence of spindles in nearly all types of muscle, the strong control exerted over them by motor areas of the cortex (60, 95), the rapidity of pathways descending to gamma-efferents (97) and, if an analogy may be used, the fact that intrafusal fibers in frog spindles are innervated by branches of the large phasic motoneurons as well as by those mediating tonic contraction (151). Even a role in adjustment of sensory perception (52) cannot be excluded since some muscle afferents project to the sensory cortex (80, 82, 191, 204).

Postural Adjustment

BASIC MECHANISMS. Postural maintenance is but another facet of the organism's efforts at homeostasis and as such is not a reflex state of wholly unvarying afferent-efferent exchange, but one in which adjustments for nuances of imbalance are continually being made. Basically, these corrections are either resistive or compensatory. The stretch reflex itself serves to resist changes in position and to encourage the return of disturbed parts (although the latter is obstructed by the lengthening and shortening reactions). The standing dog, for example, in swaying forward stretches tendons of digital flexors (physiological extensors), thus facilitating restitutive contractions of these muscles (19, 233). If the dog leans too far forward, compensatory mechanisms enter for new receptors which favor flexor action and inhibit extensor tone are excited until finally the paw is raised and replaced in a position of better support, the hopping reaction (111, 220). Resistive mechanisms are sometimes at play in operation of the 'righting reflexes'; thus the body-on-head reflex would seem to be ever ready to oppose tilting of the head. Full elicitation of righting reflexes, however, involves compensatory efforts to re-establish the postural *status quo*. The actions in which visual stimuli cause the head to turn, in which vestibular organs cause the

neck and body to be realigned, and in which the neck receptors cause the repositioning of extremities are all compensatory.

AFFERENTS IN POSTURAL ADJUSTMENT. Receptors concerned with the correction of more profound aberrations of body position are characterized by their specialized nature, such as the maculae and cristae, or advantageous location as is the case with the vestibular organs and upper cervical intervertebral joints. Receptors about intervertebral joints, particularly those where major segments of the body move with respect to one another, have important postural effects. Thus, jarring of spinous processes (51) or flexion of the pelvis on the trunk eliciting the tonic lumbar reflex in man (64, 261) and monkey (16) cause contraction of the erector musculature; flexing of the neck on the thorax diminishes extensor tonus through the vertebra prominens reflex (188); and strains imposed upon the upper three (194) or four intervertebral (217) joints lead to pronounced postural effects by means of the attitudinal reflexes and neck-upon-body righting reflexes.

It is difficult to formulate a general rule covering the effects of movements at intervertebral joints upon postural patterns. Behavior among species differs; extension of the neck in the cat causes extension of forelegs and flexion of hind legs (188), whereas in man and rabbits (187, 188) all extremities extend. The effects of movements at various levels differ; bending of the neck to one side causes extension of both contralateral extremities, whereas bending of the lumbar spinal column is said to cause protrusion of the leg and flexion of the arm (129). Additionally, some intervertebral reflexes reverse at a certain extreme of articular excursion. Moderate flexion of the neck of the labyrinthectomized decerebrate cat, for example, typically elicits powerful flexion of the neck and forelimbs, but if pressure on the head is exaggerated the neck may spring into extension (217). Similarly, but conversely, moderate active flexion of the thorax upon the lumbar region in man arouses activity in the sacrospinal muscle which at full voluntary flexion is completely inhibited (64). These effects seem generally to be bivalent in the sense, for example, that retraction of the head causes contraction of the extensor muscles of the foreparts, while bowing of the head activates the flexors (217). Also, they are reciprocal in that enhanced facilitation of extensor activity is associated with active inhibition of flexors and vice versa (85).

Neck reflexes are mediated by receptors of axial joints (194) and this is probably true for other trunk reflexes. That more peripherally located receptors also may participate in postural adjustment is suggested by the fact that the labyrinthectomized and blindfolded thalamic cat can right itself when laid upon its side or even when foot pads alone are stimulated (188). Whether this body-on-body reflex is requisitely cutaneous is uncertain as muscle receptors are not indifferent to lateral pressure upon the gross muscle (146). Indeed, spinal man shows traces of body-on-body reflexes when suspended in water (216), in which situation gravitational forces acting upon proprioceptors presumably initiate the reflex. Cues from proprioceptors, incidentally, are capable of mediating imperfect but unassisted standing in the blindfolded patient with chronic bilateral vestibular nerve section (68).

It should be mentioned in passing that it is not entirely reasonable to assume that utricular receptors, in evoking the static labyrinthine reflex, serve only the function of maintaining antigravity tone, for the position of the head which most favors extensor contractions (vertex downward) is opposite to that assumed in standing. If teleological explanations must be applied, the vestibular effects are more in the nature of a righting reflex, in which, by extension of the limbs, the body's center of gravity is displaced ventralward and righting assisted.

POSTURAL ADJUSTMENTS IN MAN. Neck, trunk and labyrinthine reflexes are recognizable in man, especially in early developmental stages (86, 247, 275), or in patients with brain damage (20, 113). In the intact adult their presence is demonstrable through use of refined methods of examination, involving either *a*) facilitation by hypertensing (276) or severely exercising the part of the body under observation (114) or *b*) detection of subtle changes in reflexes (35), muscular tension (182) or electromyographic activity (129, 261). The assistance that these reflexes may give in rational physiotherapy is becoming recognized (168, 284).

CENTRAL LEVELS OF MECHANISMS FOR POSTURAL ADJUSTMENT. Most reflexes of postural adjustment involve wide extents of the neuraxis. Labyrinthine influences, for example, are manifest in hind limbs as well as forelimbs, and stimulation of proprioceptors in the neck of the duck may affect the tail feathers (148). Some of these reflexes are complete in basic pattern at cord levels. The spinal cat or dog, for instance, when laid upon its side, exhibits those

movements of tail, rump and hind legs useful in righting, although these efforts may not succeed because of the absence of postural tone (190, 236). The central organization of other reflexes which have their afferent inflow entirely at spinal levels involves, in addition, portions of the brain stem. Neck reflexes are fully elicitable only if those portions of the brain posterior to a transection through the inferior colliculus and rostral portion of the pons are retained (201, 221). The 'center' for the body-on-head reflex is said to be in the midbrain (188, 220). Labyrinthine righting reflexes require, of course, the presence of the brain stem at the level of the eighth nerve and, additionally, the midbrain tegmentum (220). Even the lowly frog fails to develop capacity for vestibular righting when, in the tadpole, the brain stem is sectioned at such a level as to exclude the mesencephalon but leave intact the labyrinthine inflow (270). Extreme among adjustment mechanisms in the extent of neuraxis involved is visual righting, for here the cortex must be preserved (220). It is evident that complete postural performance, both for sufficiency of contractile tone and of adjustment mechanisms, requires the presence of supraspinal levels.

LOCOMOTION

Relations of Locomotion to Posture at Reflex Level

A clinician has said that "postural tone follows movement like a shadow"; and, indeed, from observation of the 'associated movements' of paralyzed limbs which accompany the use of sound limbs in hemiplegic patients, it is easy to come to the concept that all voluntary movements are accompanied by appropriate postural adjustments of the rest of the musculature (269). Locomotion and posture are even more closely related, and reflexes basic to standing contribute inseparably to progression also. The conversion of the dog leg, for example, to a rigid support by stimulation of the foot pads (positive supporting reaction) is an integral part of the protraction phase of 'marking time', or if extension-retraction is vigorous, of a 'step.' The basic reflex of posture, the stretch reflex, adds to the perfection of the locomotor pattern in limiting the ballistic excursion of limbs, preventing lurching of the body to the side of a lifted extremity, restraining antagonists in alternating contractions, etc.

Reflexes of postural adjustment also fit well into progression. For example, in man the rotation of the right side of the pelvis forward facilitates flexion of the right leg, extension of the left, flexion of the left arm and extension of the right, actions all appropriate to walking (261). To cite another example, the dog standing on one hind limb has maximum extensor tone in that leg when it is in the position most favorable for weight bearing while, conversely, extensor tone in the free limb becomes greater as the hindquarters of the dog are shoved from this stabile position, the 'Stemmbein' effect (220). This reaction fits equally well in corrective hopping or progressive stepping.

Locomotion employs, in addition, reflexes not related to posture. The 'extensor thrust', for example, although of the same sign as the supporting reaction and elicited from the same general area, differs in that it is excited best by brusque tensing or relaxing of the skin about the toe pads (238), primarily affects hip muscles rather than ankle extensors and is phasic but powerful in effect (239). Thus, the reflex is better adapted to galloping or springing (springing reflex) than standing. Opposite in sign is the negative supporting reaction which permits the leg to be lifted and, assisted by passive changes of this compound pendulum, to be carried forward in a step (19, 111, 233). Also strictly kinetic in nature are the progression reflexes which require accelerating forces acting on the semicircular canals (and in minor degree, the vestibular organs) for elicitation (44, 220); the rabbit, for example, when lowered briskly downward and forward extends its forelegs, a reaction of obvious value in bounding progression (44).

Afferent Modalities in Progression

The role of specific afferent endings in locomotion is incompletely known (79, 178, 201, 213), although the older work, as presented in the classical monographs of Magnus (187), Rademaker (220) and Creed *et al.* (43), generally indicated the importance of proprioceptors and described progression in terms of interlocking proprioceptive reflexes. Exteroceptive stimuli or volitional excitation might initially cause the head to move relative to the shoulder; then receptors in joints and muscles of the neck could initiate movements of the forelimbs; and these in turn call forth adjustments of the trunk and hind limbs. Transmission of such sequences can be purely mechanical; the hindquarters of the thoracic spinal cat may still move in appropriate diagonal sequence

in response to cues from the forelimbs (252). Or the coordination may be impressed centrally; the portion of an eel extending behind vertebral segments which have been removed or splinted against movement still contracts in rhythm with the anterior segment (99).

Reflex influences between distant limbs are demonstrable in normal (130) or paraplegic man (185, 214, 228), as well as laboratory animals (213, 252). Typically, the pattern is diagonal, and pressure to one forepaw of the cat (decerebrate) with elicitation of flexor withdrawal causes the opposite forelimb and ipsilateral hind limb to extend while the other hind leg flexes (237). If alternate flexion and extension are imposed on the forelimbs, stepping of the hindquarters in appropriate diagonal sequence may occur even in the bilaterally deafferented hind limbs (252). It is surprising that group I afferents from muscles of the forearm are apparently not concerned in causing extension of the ipsilateral hind limb and that electrical stimulation only of group III or smaller fibers causes such extension (178). This is a poignant reminder that little is yet known of the physiological role of the smaller afferents in muscle.

Inconsistent with this general pattern of response obtained upon electrical stimulation of forelimb nerves is inhibition of the flexor longus digitorum muscle of the hind limb during stimulation of group II muscular or cutaneous afferents from extreme distal portions of the forelimbs (178). This inhibition of a single physiological extensor in a generally extending limb has presumably the purpose of preventing protrusion of the claws. It, interestingly, is mediated by rather direct connections, the inhibition of the monosynaptic response of the flexor digitorum motoneurons appearing as briefly as 2.5 msec. after stimulation of a brachial trunk (178).

Reflexes of locomotor significance also exist between companion limbs. Passive or reflex flexion of one hind leg, for example, causes crossed extension of the opposite one in the cat and dog (212, 213) and also in man (130, 228) and, conversely, passive extension of the contralateral thigh leads to crossed flexion of the hip (241). Even within a single limb the afferent influx from individual contracting muscles favors locomotor patterns. Contraction of the cat hamstring muscles, for instance, induced by stimulation of the appropriate ventral root, causes prompt inhibition of decerebrate or crossed extensor tonus in the vastocrureus, which has its motor outflow at a different spinal level (41). Reciprocal contraction of flexors and extensors is, of course, basic to locomotion (122, 240, 244), although this does not mean that augmentation and diminution of contraction may not proceed concurrently in antagonistic muscles during portions of the walking cycle (221). Such graded restraint by the relaxing muscles makes movements smoother (122).

The importance of cutaneous receptors in induction of locomotion is probably secondary. The eel, completely devoid of skin, still can swim (99); pigeons (34) or cats (30) in which nerves are severed at the ankle display only a trace of abnormality in their gaits; and, as is well known, the spinal dog steps more readily when held aloft than when its feet are in contact with the ground (30). The dog may even cease stepping bilaterally upon touching one foot to a supporting surface (240). On the other hand, the monkey which is deprived of cutaneous sensation at the apex of an extremity shows disproportionate loss of use of that extremity, while he suffers little disability if, by section of selected dorsal roots, cutaneous sensation is spared but muscles deafferented (203, 265).

Periodicity of Locomotion

The intriguing question has been raised as to whether the periodic pattern characteristic of progression derives ultimately from an oscillation autochthonous to the central nervous pathways (266, 274) or requires for its generation reverberating circuits through participating muscles or limbs (100, 172, 173). That supraspinal structures may not be requisite for rhythmic patterns is evident from the stepping of the decapitate cat (240) and the chronic spinal dog (49, 193) or, more spectacularly, from the independent and spontaneous rhythms of the two cord segments of the dogfish in which the cord has been transected at two levels. Various central phenomena, such as rebound, accommodation and reciprocal action between motor centers, no doubt contribute to the production of rhythmicity but do not of themselves indicate whether it is fundamentally central or peripheral. Certain spontaneous rhythmic variations in pyramidal tract discharges (277) or in monosynaptic reflex responses (183, 184) do not seem to bear any simple relation to locomotion.

LOCAL AFFERENTS AND RHYTHMICITY. A peripheral basis for reciprocating contraction lies in the changing composition of afferent inflow arising in any muscle which is allowed to contract against yielding resistance. During flexion of the leg, for example,

the discharge from annulospiral endings in the passively extending thigh muscles is increased, with resultant growing facilitation of the same and synergistic muscles and suppression of flexors. Extensor contractions finally appear. Then, as thigh extensors actively shorten, endings in the spindles become unloaded while the discharge from tendon organs increases, thus weakening the extensor contraction and setting the stage for the next cycle. Hence, in theory (and neglecting an active role of gamma efferents) might be explained the reciprocating contractions of a pair of opposing muscles in an otherwise denervated leg (30, 32, 243). Not only would such swings in composition of afferent inflow favor alternation at the spinal level, but cerebral (83, 271) and cerebellar (147) cortices would be predisposed toward movement of the opposite sign, a net result which has been referred to as a 'reversal effect' (43).

DISTANT AFFERENTS AND RHYTHMICITY. Local circuits are not essential for repetitive movements as these can occur in deafferented whole limbs or single muscles (13, 31, 170). In elicitation of the scratch reflex, for example, irritation of a small skin focus over the shoulder of the dog may call into rhythmic play some 19 muscles of the hind limb despite the absence of all dorsal roots to the extremity (245). Also, the deafferented hind leg of the cat may participate fairly effectively in progression under the changing excitement of influences from other moving parts (252).

In the toad a diagonal pattern of leg placement characteristic of normal walking is retained if one, two or even all four extremities are deafferented (274). In fact, vestiges of diagonal progression remain so long as the dorsal and ventral roots of any one segment are intact, even though this innervates anal regions (101). Deafferentation of this last segment abolishes the diagonally coordinated movement. From this and experiments on other forms, Gray & Lissman have come to the view that an external circuit must be intact for the appearance of periodic movements of progression. Others using tadpoles (274) or teleosts (266) deny such dependence. Certainly in mammals comprehensive deafferentation prohibits rhythmic movements except under extreme conditions, such as cutting or electrically stimulating the spinal cord (31, 32). Pollock & Davis (219), for instance, prepared chronic cats in which the first 18 to 23 pairs of dorsal roots were severed and which terminally were subjected to decerebration and to severance of the cord beneath the last deafferented segments. No movements were seen in the upper part of the body, whereas the hind limbs promptly exhibited stepping. In mammals even more restricted deafferentation can impair participation by an extremity in locomotion. If the cat foreleg is deafferented, its efforts in progression are feeble and quick to fatigue (163); and any extremity of the monkey is severely incapacitated by deafferentation, although 'associated movements' may persist (162, 163, 203). That the residual progressive movements remaining in deafferented limbs result from sensory barrages elsewhere is indicated by the fact that, if the sound limbs are prevented from moving, the operated leg is incapable of movement even if the animal is enraged, as Sprong (252) demonstrated for the cat. This would, incidentally, point to joint receptors as the sensory terminals concerned, for muscle and tendon receptors would be markedly affected in the restrained leg. Patients, in contrast, may exhibit associated movements with contractions of sound extremities in which there is no actual excursion, as in the handclasp (269).

BACKGROUND FACILITATION AND RHYTHMICITY. Although the puppy which has undergone section of the thoracic spinal cord in the early days following birth is said to be capable of walking, turning, climbing and even jumping (246), the hindquarters of the puppy (263) or monkey (264) which are isolated from suprasegmental influences and additionally deafferented evince no overt spontaneous activity. The suspended spinal dogfish, a preparation which exhibits tireless swimming activity, is still spontaneously active if one half its dorsal roots are cut, capable of short-lived rhythmic movement upon stimulation if only one pair of sensory roots remains, but utterly quiescent if all 65 roots are cut (104, 173). These results and the arguments of the last section appear to refute the idea that the rhythmic activity characteristic of progression arises in the cord. However, such experiments are not conclusive, as the background of facilitatory nervous activity is also reduced. The progression of chronically deafferented toads, for example, is more sluggish and easily fatigued the greater the extent of deafferentation (100, 274). Furthermore, the relationship is not linear as the effect of cutting the dorsal roots to all limbs is markedly greater than one would expect by simply adding the effects of separate fore- and hind-limb deafferentation (100, 274). Under these circumstances it is conceivable that a locomotor pattern of

activity is still present centrally but is incapable of overt expression. Such hidden events in mammalian gamma efferent circuits during complete absence of alpha activity are commonplace (57). Rhythmic alternation in ventral roots of positive and negative slow potentials, which are usually associated with extensor and flexor responses, respectively, have been observed in deafferented lumbosacral segments in the absence of contractions (13, 14).

Gray & Lissman (100) would seem to have overcome the above objection. As mentioned already, they found that the toad left with intact dorsal roots to only one of its limbs was capable of feeble but coordinate ambulation in all limbs. If then further roots were sectioned, this time the ventral roots to the limb with intact afferents, no progressional movements were elicitable. Conversely, if three limbs were de-efferented without disturbing the afferents, while in the fourth limb dorsal roots alone were cut, only monophasic movements of retraction were obtainable (101). These observations seem to prove for this animal the experimenters' thesis that the reciprocating movements of diagonal progression are initiated and paced by a reverberating circuit between the extremity and the cord.

RHYTHMICITY AND NEURAL BALANCE. Not all locomotor movements are abolished in the toad in which all dorsal roots are cut, for the hind legs may still engage in symmetrical swimming movements (100) which disappear only following destruction of the labyrinths (103). Both diagonal and symmetrical progression patterns are apparently intrinsic to the mammalian cord also, the symmetrical pattern being more resistant as it alone may remain during early recovery from cord transection (32, 193), asphyxia (32), alcohol intoxication or aeroneurosis in man (130). The rabbit is instructive in this respect for the intact or thalamic animal has hopping progression but, after spinalization, stepping, marking time and crossed extension reflexes are prominent (164). This and the deafferentation experiments upon toads suggest that strong and symmetrical supraspinal influences mask inequities in the effects of afferents entering from the two sides at the spinal level. In accord with this, elimination of the powerful labyrinthine influence increases markedly the incidence of running in the decerebrate cat (217).

Probably of decisive importance in determining whether symmetrical or diagonal coordination will prevail is the degree of balance that is struck between influences impinging upon the two sides. The decerebrate cat, in which stimulation of sensory nerves (30, 243) or cord surfaces on the two sides (245) is carefully equated, may gallop, although usually an unbalanced state of 'double reciprocal innervation' obtains and stepping emerges (242). Such nicety of balance may be unobtainable in the whole animal; thus, it was found impossible to adjust the toad hind limbs on a drum so that rotation of the drum caused other than alternate replacement of the limbs (102).

Many observations indicate the necessity of a near balance between flexor and extensor influences for the appearance of alternating movements (43). Induction of stepping in a leg or pair of antagonistic muscles by stimulation of two sensory nerves of opposing effect (31, 66), or by matching a flexor reflex against a background of extensor rigidity, requires a certain optimal intensity of stimulation (14, 31, 66). The decerebrate cat, while recovering from the ether, shows running actions which, with the onset of extensor rigidity, are occluded. Similarly, the decerebrate alligator when provoked to movement has initially sufficient balance between flexor and extensor groups to permit progression, but the stimulation of walking itself disturbs this balance and after a few steps, the animal halts in extreme extension, unable to progress further (5). The worsening of progression in the spastic patient when very active is perhaps a comparable phenomenon.

In a similar vein, but of greater functional interest, is the observation that, while in the labyrinthectomized and anemically decerebrate cat ventroflexion of the head elicits strong forelimb flexion and dorsiflexion of the head brings on extension, an intermediate position sponsors rhythmic movements of the forearms (217). This intermediate pose is, of course, that in which the walking animal naturally carries his head.

It is in regard to the balance of flexor and extensor influences that a guess may be made as to one function of flower-spray endings. At low tensions of muscle, annulospiral endings are proportionately more active than flower-spray afferents, so that relatively pure facilitation occurs and some degree of antigravity tone is produced unopposed. At higher stretches flower-spray discharges enter and a flexor influence arises. Thus, a neural balance in the afferent discharge impinging on the homonymous motoneurons is set up which other incident influences may easily send into rhythmic activity. Tendon organs, the discharge of which appears at even higher tensions, may serve the somewhat different

purpose of modulating the excursion of the muscle and so protect it against strains.

It is not readily apparent how rhythmic alternations are engendered under flexor and extensor influences of unvarying potency as, for example, under simultaneous and steady stimulation of skin nerves of contrasting effect. Perhaps the alternation arises through a difference in accommodation of the two central pathways. Flexor motoneurons, at least in the decerebrate preparation, fire easily to single-shock stimulation of appropriate nerves, but their discharge dies out quickly and cannot be driven at rapid frequencies (3, 74). Extensor neurons, on the other hand, are facilitated and sustained by repetitive afferent stimulation. Thus, under constant afferent inflow, flexor activity would be favored initially, the balance of effect then turning to extensor activity. Final reversal of the cycle might then appear through long-term accommodation of the extensor pathway, aided by shifts in composition of the afferent inflow.

Additional Effects of Afferents upon Locomotion

DEAFFERENTATION ON PRECISION OF MOVEMENTS. Deafferentation produces defects in locomotion which are separate from those resulting from loss of supporting tone or impaired rhythmicity. The cat with a chronically deafferented hind limb can use the leg effectively in walking although with some abbreviation of the weight bearing phase of the step (252). When running, the absence of myotatic reflexes in that leg becomes less important relative to the deluge of impulses from remote moving parts, and the limp may be unnoticeable. However, the leg oversteps and, in general, participates more vigorously than on the intact side (252). This is to be expected as, in the deafferented hind limb of a cat, segmental reactions including stepping (243) are markedly more abrupt in onset, decline and total excursion than those of the intact limb (217, 223, 237, 241, 252). Among factors which may contribute to this hyperreflexia are: *a*) the loss for the actively contracting muscle of inhibitory effects from tendon organs, whereas loss of facilitatory effect from these tension-sensitive organs in the passively tensing antagonist would be much less (6); *b*) the absence, on one hand, of 'unloading' of spindles in actively shortening muscle and, on the other hand, of augmenting discharge from the passively extending antagonist, both actions which, from a consideration of annulospiral effects, tend to restrain alpha activation; and *c*) the absence of dampening contractile tone. Modulation by the cerebellum and other higher central structures, which is dependent upon sensory information, of course, is also lacking. Lastly, caution should be exercised in ascribing hyperactivity in the chronically prepared limb directly to loss of neuronal circuits, for neurons deprived of afferent inflow become sensitized (257).

Coupled with the hypermetria of the deafferented hind leg of the cat is a lack of precision and corrective ability in placing the foot. Stalking along the rungs of a ladder becomes impossible, and in walking the cat often steps on the dorsum of the paw (163, 252, 262). In part, this malpositioning of the foot may be a consequence of the fact that muscles about the ankle and foot participate less completely in postural tone than more proximal muscles (19, 203, 217, 226, 237), a provision which permits the paw to adjust to inequalities of the ground by more local reflexes. Movements appropriate to such function, for example, are demonstrable in the foot of the paraplegic patient which, if stroked on the outer side of the plantar surface, may evert; if on the inner side, invert (228). In part, also, improper use of the foot may result from loss of less localized 'placing reactions.' In either case deficits in placing the foot result as well from local deafferentation below the ankle as from cutting all dorsal roots to the limb, as shown in the forepaws and hind paws of cats and dogs by Sherrington (241).

EFFECT OF AFFERENT INFLOW ON MODE OF PROGRESSION. The mode of progression of an animal is sometimes dependent on the nature of the afferent inflow entering at segmental levels. Toads, for instance, when floating freely, exhibit swimming movements exclusively. When one foot encounters resistance, however, the leg stiffens in a 'retractor extensor response' and other limbs move into a pattern of diagonal progression (102). The same toad placed upon moist ground engages in burrowing, a reaction which is lost following deafferentation of the legs (274). Even visceroceptors may influence locomotion, for in the carp discharges from the swim bladder affect the set and stroke of the pectoral fins (149).

Brain and Locomotion

Animals vary greatly in their ability to maintain locomotory movements after the spinal cord is cut (212). Chronic spinal tadpoles are incapable of

spontaneous translatory movements even when the cord is cut before hatching (270). Spinal dogfish, on the other hand, exhibit tireless spontaneous swimming, although similar preparations of eels or other teleosts are quiet unless prodded (166, 172). Cats, dogs and rabbits with cervical cord transections exhibit spontaneous running, although no complete progression (240). Effective stepping of the adult cat hindquarters, however, may be obtained even in the absence of cues from the forelimbs, providing the cord has been transected at an early age and physiotherapeutic care is given (246). Monkeys demonstrate alternating reflexes only in the tail (236); and in spinal man, stepping is not found in the presumably favorable period of 'neural balance' between early flexor and later extensor rigidity (158, 227). It is evident that in most vertebrates contributions from supraspinal levels are essential for effective progression and, in some, even for production of the alternating rhythms basic to progression.

The cat, in which the brain stem is cut so as to leave only the medulla in continuity with the cord, has flaccid muscles and little spontaneous activity (258). Tone, on the other hand, is prominent but movements are in abeyance when the section just spares Deiter's nucleus and portions of the facilitatory reticular formation (164, 240, 258). When the decerebration is made yet more rostralward, as by rendering anemic parts of the brain anterior to a plane passing behind the red nucleus extensor, muscular tone although subject to exacerbations is often more nearly normal and then may be interrupted by fits of running (217). Lastly, when the section passes rostral to the superior colliculi and down to the optic chiasma so as to spare the red nuclei, subthalamus and portions of the hypothalamus, the cat can rise to its feet and walk normally along a straight line with the body well-supported and coordinated (164, 220). Particularly if the animal is young, these movements may not be distinguishable from those of an unoperated animal of the same age (280). When, however, such a cat encounters an obstruction, it acts like an automaton, the head remaining pressed against the obstacle while the legs continue to walk (164). Thus, reflex mechanisms of progression are essentially complete, but behavioral defects are prominent.

The question arises whether the lack of locomotory movements in the classic decerebrate or in the medullospinal animal is a result of the supraspinal influences throwing the 'neural balance' between flexor and extensor tendencies too far off to permit alternating activity in the motor pools to develop. Certainly in adult cats progressive movements seem to be lost when, upon successive removal of higher brain structures, rigidity first appears (164, 196); and in chronic decerebrate cats running reappears as the hyperextension diminishes (170). Progressive activity is plentiful in the decerebrated puppy, kitten (102, 280) or rabbit (102, 159), preparations in which rigidity is inconspicuous. Furthermore, the opossum, which has perhaps less encephalization of locomotory functions, is capable of well-coordinated progression, despite the presence of concurrent rigidity produced by a section just anterior to the inferior colliculi (273). These observations suggest that the brain stem may itself produce rhythmic activity as distinct from merely impressing extensor and flexor influences of constant tenor upon intrinsic rhythmic mechanisms of the cord. Related, but not conclusive, evidence on this point is the finding that single-shock stimulation of the medulla may arouse rhythmic activity in the deafferented lumbosacral cord (13).

Progressive activity of the hind limbs is more independent of cephalic control than is that of the forelimbs (239, 240). The rabbit with a low brainstem transection, for example, will upon stimulation of an intercostal nerve exhibit bilateral movements of the hind legs in complete absence of effects on the forelimbs (164). Similarly, no amount of goading can make the forelimbs step in a pontine cat, although the hindquarters do so readily (190).

Tied in closely with the question of reflex capacity for effective locomotion are certain facilitatory relations of the cortex to movement. The thalamic cat, although capable of essentially normal progression, appears reluctant to move and remains in a normal sitting posture for long periods. In monkeys, basic motor performance is more dependent upon higher centers and thalamic animals seem incapable of progression; a mere loathing to move in the presence of ability for locomotion appears, however, following extirpation of certain cortical areas (211). Cortical lesions impair the ability of rats (27), rabbits (28), cats (8), dogs (283) and monkeys (211) to place the extremities properly upon supporting surfaces in response to tactile stimulation (placing reaction) or to make corrective hops when body balance is imperiled (hopping reaction). To some degree this loss may result from absence of such facilitatory influence rather than a loss of an essential site of integration of these reactions. Placing of a sort, for

instance, is said to be demonstrable in the pontine cat under amphetamine administration (190), and in the hind legs of cats spinalized at a very early age (246). In the opossum where cortical concern with posture is less developed, hopping reactions are still retained to some extent after decerebration (26).

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Central control of eye movements

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CHAPTER CONTENTS

THE MOVEMENT OF THE EYES is brought about by the extraocular muscles. These movements are extremely rapid and the eye muscles are much the most rapidly acting in the body. Correspondingly we find a series of anatomical and physiological specializations by which this speed of movement is attained. Their movements are not only very quick but also very precise. Again we find anatomical and physiological mechanisms adapted for precision of movement. Perhaps the most striking feature of eye movements is the extent to which they are under the control of the highest centers of the nervous system. Correspondingly we find little or no local reflex activity; however, close relations exist with the balancing mechanisms of the head and with the very complex mechanisms by which retinal stimuli in particular, and many other stimuli to some extent, can give rise to precise and appropriate eye movement.

Much of the physiology of the mammalian limb muscles has been worked out on the cat, but to confine the work on eye muscles to the study of a limited series of the more usual laboratory animals has in the past sometimes proved not only unhelpful, but misleading. A much wider comparative study of these cranial muscles reveals species differences that are often of great value in helping to elucidate the main problems. The four recti and two obliques are found in all vertebrates from fish to man, but the degree of eye movement they are called on to bring about varies enormously. For work on the eye muscles sheep and goats have recently proved to be valuable (36) for these animals possess many typical sensory endings, i.e. muscle spindles, in their eye muscles (31) and they also have discrete sensory nerve trunks leaving these muscles (146, 150, 151).

ANATOMICAL CONSIDERATIONS

The anatomy of human eye muscles has been adequately described elsewhere (60, 145). Their actions are given in detail in most textbooks of ophthalmology, while textbooks of physiological optics deal with the nature of the movements in secondary and tertiary positions. Their comparative anatomy has been described by Duke-Elder (60) and by Wolff

(153) and only special points will be mentioned here. The insertions of the muscles are near the equator of the eyeball in man and the primates where there is considerable eye movement; in other mammals the insertions may be much closer to the cornea and in birds they are nearer the optic nerve. In some animals, particularly the ungulates, the superior oblique muscle is fleshy throughout its course, it passes through a wide trochlea and the muscle fibers extend almost to the insertion; in birds this peripheral portion forms the whole muscle which has its origin just dorsal to the origin of the inferior oblique. The sixth nerve innervates the lateral rectus muscle, but numerous mammals have a cone or slips of a retractor bulbi muscle inserted behind the equator of the eyeball and also innervated by this nerve. The muscle pulls the eye back into the orbit and this activity is apt to be overlooked by physiologists working in this region. It can be seen very clearly in carnivores and ungulates when the recti are cut. In birds the quadratus and pyramidalis, also innervated by the sixth nerve, are attached in a similar position and serve to draw back the nictitating membrane. In some fishes the lateral rectus has the peculiarity of having its origin in the neck.

Muscle Fibers

The fibers of human eye muscles vary from 10 to 50 μ in diameter (141, 152) and they run the whole length of the muscles. The fibers are somewhat smaller in the cat (7 to 35 μ) and monkey (5 to 40 μ) (44). In the goat they are 10 to 85 μ. Fibers of large diameter tend to be collected together forming a central core in the muscles, while fibers of small diameter form an outer coat, especially at the lateral edges and on the surface away from the eyeball. This arrangement is particularly striking in human and monkey material and is seen also to a lesser extent in the cat and goat (42).

Motor End Plates

In man there is a conspicuous compact band of motor end plates at the junction of the proximal and middle third of a rectus muscle (33). One of these end plates is illustrated in Daniel (48). The motor end plate band is also conspicuous in the monkey, but the end plates are more widely scattered in the cat and goat. Other typical motor endings are found in the outer coat of fine muscle fibers. They often consist of a single small motor end plate at the end of a fine nerve fiber.

Muscle Spindles and Other Receptors

The afferent endings in limb muscles are the muscle spindles, tendon organs and some fine naked endings. In the eye muscles every part of the muscle is richly supplied with nerve fibers, and in most species, apart from the main motor end plates, the endings are not typical, nor has it so far proved possible to cut a purely motor nerve to the muscles so as to leave the sensory endings intact. Thus much confusion has arisen about the sensory endings, the literature on which is surveyed by Tiegs (135). All the mammalian eye muscles examined by silver and gold impregnation or methylene blue techniques show a rich innervation of both origin and insertion tendons, with small nonencapsulated tendon endings near the musculotendinous junctions (33, 42, 136). Muscle spindles in the eye muscles were first seen by Crevatin in the ox (45). Cilimbaris (31) gives a detailed description of them in the sheep; he also counted them, finding over 200 spindles in a single inferior rectus muscle. Cooper *et al.* (36) found about 120 in a goat inferior oblique muscle. It is now clear that typical muscle spindles are very numerous and universally found in the eye muscles of the artiodactyl branch of the ungulates. Their presence in man was denied for many years, but search through serial sections showed them to be present in considerable numbers (up to 50) in the proximal third of all the muscles, with a few scattered ones peripheral to the band of motor end plates (33, 106). Spindles were also found in the chimpanzee, but not in the monkey (33).

The muscle spindles in human eye muscles (fig. 1) have a very thin connective tissue capsule; they lie near the outer coat of small diameter muscle fibers so that the intrafusal muscle fibers are only a little smaller than the adjacent extrafusal fibers. The intrafusal muscle fibers have some central nuclei, but so far no nuclear bags have been seen. They recall the smaller intrafusal fibers seen in the tenuissimus spindle of the cat (20) and in the lumbrical spindles of man (34).

In the eye muscles of man, some of the larger nerve fibers take several spiral turns round large muscle fibers, in the core of the muscle just distal to the motor endings, and then end on these fibers (48). Occasional nerve fibers have been seen en-

FIG. 1. Longitudinal section through a human inferior rectus oculi muscle. A muscle spindle is seen crossing the field from top to bottom. The delicate capsule of this spindle is torpedo-shaped and encloses at least two intrafusal muscle fibers. These are of smaller diameter than the adjacent extrafusal muscle fibers and are separated from the capsule by the periaxial space. A small nerve trunk is seen at the *upper right part* of the field. This runs down to enter the spindle almost at its mid-point. A capillary runs along just inside the capsule on the *left*. Paraffin section; Masson's trichrome stain. [From Cooper & Daniel (33).]

circling muscle fibers in the cat (42, 110). Accessory nerve fibers given off from fibers going to motor end plates are described in the rabbit (81, 154). These fibers may run for some distance along a muscle fiber giving off fine endings at intervals. Other nerve fibers, which show no connection with the motor fibers, also run along the small muscle fibers giving off twigs to fine endings at intervals (81, 148). Some of these fibers are probably sensory, but those linked with the main motor supply must be motor and they may form a device for shortening the rising time of the muscle twitch.

No detailed analysis of the behavior of the nerve muscle junction in the eye muscles has yet been made. Such analysis might prove interesting as these muscles have the property of contracting in response to acetylcholine, a contraction due to bursts of action potentials and not to contracture (24). This effect persists in the eye muscles *in vitro* (69). It is not known whether the large and small muscle fibers behave differently in this respect. Skeletal muscles on the other hand only contract with close arterial injection of acetylcholine.

Motor Units in Eye Muscles

The very rich nerve supply to these small muscles suggests a small motor unit, i.e. with a low ratio of motor nerve fibers to muscle fibers. Counts of the nerve fibers supplying the eye muscles and of the muscle fibers were made for human extraocular muscles by Bors (18) who obtained ratios varying from 1:4 to 1:7. His nerve totals appear low, judging by counts made by other observers (16) but, as he takes no account of possible sensory fibers, 1:6 may be about the size of a human eye muscle unit; a motor fiber can often be seen to divide into a little cluster of 4 to 6 end plates on neighboring muscle fibers. A count of nerve and muscle fibers was made for sheep eye muscles by Tergast (133). He presumably counted the nerve fibers in the main nerves to the muscles and did not include the separate sensory trunks (see below). Thus in all the muscle nerves except that to the inferior oblique he would be counting mainly motor fibers and his ratios of 1:6 to 1:10 may give the size of the motor unit in these animals. His lower ratio of 1:3 or 4 for the inferior oblique may well be explained by the fact that the main nerve to this muscle is now known to be a mixed nerve until very close to the muscle.

Nerve Fiber Size

In assessing the sizes of nerve fibers supplying a muscle, consideration must be given to the age of the animal and the amount of shrinkage due to the technical methods used by the author. Old and young animals tend to have a unimodal distribution of fiber sizes (118). Distribution curves for the nerve fibers to extraocular muscles of adult man are given by Bjorkman & Wohlfart (16) for nerve trunks near the brain and by Rexed (118) near the muscles. A bimodal distribution is described with maxima at 4 to 5 μ and 9 to 10 μ, the largest fibers being about 13 μ (16); but the maxima are not obvious. Bjorkman & Wohlfart also give figures for the sixth nerve in the cat, dog, cow and sheep. Rexed gives them for the fourth nerve in the rabbit and Fernand & Young

(63) for muscle branches of the third nerve in the rabbit. In the young goat the fourth nerve, where it is mainly motor, shows a fiber range of 2 to 18 μ with maxima at 6 μ and at 12 μ. In the small trunks of purely or mainly afferent fibers the range is from 2 to 14 μ, with a unimodal distribution and a maximum at 8 μ (Donaldson, G. K., unpublished observations). The numerous larger fibers in the motor nerve may be accounted for by the numer of fibers needed to supply the large number of motor units, since the motor unit is so small. The number of spindles in the muscles leads one to expect that the elevation with a maximum at 6 μ consists of small gamma efferent fibers. As in the limb muscles, one of these nerve fibers supplies several spindles, and at least three motor fibers supply each spindle (147).

TIME RELATIONS IN EYE MUSCLES

In cat eye muscles the single twitch takes about 7 msec. to reach its peak and 15 to 20 msec. to subside. In the goat it reaches its peak in 9 msec., and takes about 40 msec. to relax. The twitch tension is about 9 gm for the medial rectus in the cat and about 50 gm for the inferior oblique in the goat. The maximal tension in tetanus is 100 gm in the cat and approximately 250 gm in the goat (36, 41). The tetanus tension ratio for the cat is 1:10, much higher than for skeletal muscles. This is to be expected in view of the short twitch duration. The frequency of stimulation required for complete fusion in the cat is 350 impulses per sec. (41). In the goat 250 impulses per sec. gave almost complete fusion.

The first measurements of the natural rate of motor unit discharge in eye muscles were made by Reid (117). In view of their high fusion frequency, units were expected to discharge at much higher rates than the 20 to 50 per sec. found in skeletal muscles by Adrian & Bronk (1). Reid (117) found rates up to 160 per sec. in cats and goats. Similar rates were found in human eye muscles by Björk & Kügelberg (14) and in bird eye muscles by Sommer & Whitteridge (127). It is interesting that ocular motoneurons may not possess recurrent collaterals which in the case of spinal motoneurons are distributed to the Renshaw cells (115). It is believed that the Renshaw cells provide a mechanism which limits the rate of discharge of motoneurons, presumably to some value near the fusion frequency of skeletal muscles (61). In the eye muscles the muscle fibers can probably respond by increased tension to the highest frequency of discharge of which motoneurons are capable. According to Björk & Kügelberg (15), there is a considerable resting discharge in all the eye muscles of man with the eye in the mid position. During slow movement as one muscle contracts the motor discharge in its antagonist decreases, to reach its minimum at the extreme of movement. During rapid movement the antagonist muscle relaxes completely at the onset of the movement (13). There is no definite evidence of 'checking' action to halt a movement. In paresis the rate of discharge of surviving units may be as high as 200 per sec. (15).

AFFERENT DISCHARGES FROM EYE MUSCLES

Afferent discharges from the eye muscles of the dog were reported by Cardin & Rigotti (28). Similar discharges were recorded in fibers of the third nerve coming from the inferior oblique muscle in the goat (36), and these latter studies were continued by leading from single fibers in the separate afferent nerve trunks (35, 146), often with the motor nerves intact. The response to passive stretch of the muscle is similar to that given by the A endings in limb muscles described by Matthews (102), and in each case a muscle spindle ending was considered to be the unit giving the discharge. Such a response appears in figure 2. The discharge shows considerable irregularity while the motor nerve is intact but great regularity after it is cut. This may be due either to discharge in neighboring extrafusal fibers or more probably to contraction of intrafusal muscle fibers. A twitch elicited by stimulation of the motor nerve causes a pause in the discharge rate during contraction, often followed by a burst of impulses in relaxation. There is sometimes an early single impulse due to electrical or mechanical events at the onset of contraction (cf. 93). When the motor nerve is intact, identification of the effects of the intrafusal fibers is made difficult by the continuous background discharge of α motoneurons under most conditions. If, however, the motor nerve is split up, it is possible to obtain a slip, nerve stimulation of which gives no mechanical contraction, but produces a large increase in the discharge of afferent fibers from a spindle. Stimulation of this gamma motor fiber by 10 stimuli in 5 to 10 msec. gives a burst of afferent impulses of up to 350 impulses per sec. Stimulation

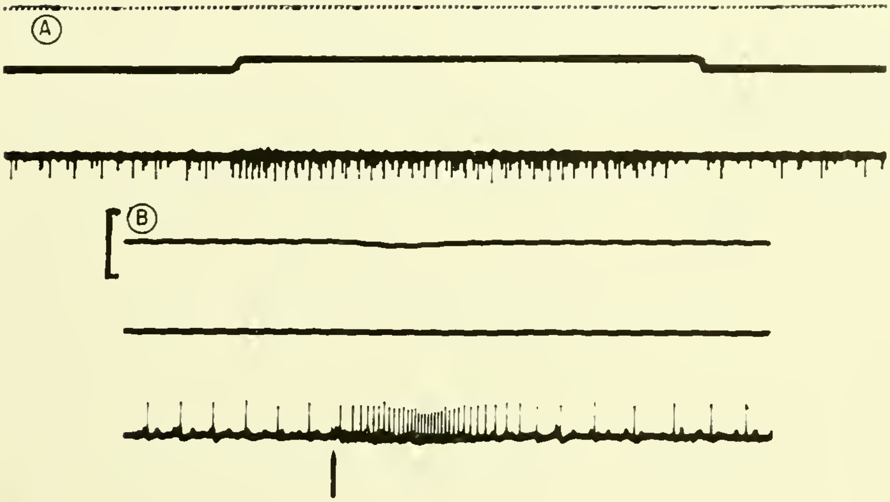

FIG. 2. Action potentials of an afferent fiber from a muscle spindle in the superior oblique of the goat. *A*. Effect of pulling on its tendon: *upper record*, time in $^1/_{10}$ and $^1/_{100}$ sec.; *middle record*, signals of active stretch; *lower record*, action potentials in one large and several small fibers. *B*. Effect of stimulating the nerve supply to the intrafusal muscle fiber: *upper record*, tension (calibration, 5 gm); *middle record*, 50 cycle time marker; *lower record*, action potentials from a single muscle spindle; *arrow* marks the stimulus artefacts. [From Whitteridge, unpublished observations.]

of the gamma efferent at about 100 impulses per sec. may increase the sensitivity of a spindle receptor to stretch by a factor of 7 to 8 (147).

Single unit discharges have also been recorded in fibers from cat and monkey eye muscles (42). The discharges during passive stretch resemble those from muscle spindles and give proof of low threshold stretch receptors in these muscles. Technical difficulties prevented observation of the effect of a motor twitch on these discharges.

Responses from tendon endings in goat eye muscles have also been recorded (35). Their discharge is similar to that of the B endings described by Matthews (102). They discharge, often with an increased burst of impulses, during the rising phase of a muscle twitch. Their threshold to stretch may not be higher than that of muscle spindle endings, but their response to rate of change of stretch is comparatively slight. During steady stretch the discharge is regular both when the motor nerve is intact and when it is cut.

FIG. 3. The orbit of the goat seen from above to show the afferent branches. *II*, optic nerve; *IV*, trochlear nerve; *V*, part of ophthalmic division of trigeminal nerve; *r*, levator palpebrae; *d.s.*, rectus superior; *g.o.*, superior oblique; *n*, branches of the nasociliary nerve. [From Winckler (151).]

Afferent Paths From Eye Muscles

It is now well established that the eye muscles can send afferent discharges to the brain (40) and it is of interest to know the pathway taken by such discharges. Reference has already been made to the special afferent nerve trunks from the eye muscles in sheep and goats (fig. 3). These were first seen by Winckler (149–151) who found that they ran from the muscles to the ophthalmic or rarely to the maxillary division of the fifth nerve in various ungulates. The work was confirmed and extended to other ungulates, birds and reptiles by Kiss (91). These trunks are usually completely separate from the motor nerves but in a few instances join the motor

nerve for a short part of its course. The main nerve from the inferior oblique muscle starts by being mixed, but a branch to the fifth nerve leaves the motor nerve as it winds round the lateral edge of the inferior rectus. The proximal afferent branch from the superior oblique runs with the fourth nerve for a short distance before leaving to run with other, usually three, branches from the more distal parts of the muscle to the fifth nerve. A few very fine branches have occasionally been seen in the orbit of the cat running from the fourth nerve to the fifth (148); Cooper, as reported in Cooper *et al.* (40), was able to lead from such a branch and obtained a sustained discharge in response to stretching the superior oblique muscle. Connections between the eye muscle nerves and the fifth nerve are more commonly seen in the cavernous sinus. They were reported in man and described by Stibbe (129); they have also been seen by Cooper (unpublished observations) in a number of animals.

So far no unequivocal afferent discharge has been detected in the intracranial portions of the third and fourth nerves, either in the goat (Daniel & Whitteridge, unpublished observations) or in the cat (Cooper, unpublished observations), although those nerves certainly contained excitable motor fibers while the existence of afferent fibers was being tested. One might conclude that afferent fibers in the goat and cat which may enter the central nervous system by the motor nerves, if they exist at all, must be of very small diameter; but the question is by no means settled. Fine degenerating fibers in the medial rectus of the monkey found by Tozer & Sherrington (136) after section of the ophthalmic branch of the fifth nerve are almost certainly due to afferent fibers which leave the third nerve trunk to reach the fifth nerve. On the other hand Tozer & Sherrington inferred that the majority of afferent fibers from the eye muscles run into the central nervous system by the motor nerves, in view of the persistence without degeneration of large numbers of fibers which run to the musculotendinous junction and seem to be afferent in nature. It is just possible that these fibers in fact reach the motor root of the fifth nerve by filaments which pass deep to the semilunar ganglion and might therefore not have been cut with the ophthalmic division of the fifth. Except in the ungulates, all the branches so far investigated running from the eye muscles to the fifth nerve are small and it is difficult to see how they can supply all the sensory endings in the muscles. Wilkinson (148) emphasizes this point in the cat. There is a considerable histological literature on fibers from the mesencephalic root of the fifth nerve which are said to join the motor nerves in their intracerebral course (132).

A search of the brain stem of the goat with a microelectrode gave good evidence of primary neurons giving rise to the afferent endings in the extraocular muscles. These neurons were located in the pons close to the point of entry of the fifth nerve (37), as shown in figure 4. Enough responses were also obtained from cells of the mesencephalic nucleus of the fifth nerve in the midbrain to establish that these primary afferent fibers have their cells of origin in this nucleus, as do the fibers from the proprioceptors in the jaw muscles (43). Secondary neurons excited by proprioceptors in the eye muscles have been found in the central tegmental tract, the deeper layers of the superior colliculus, the posterior commissure, pathways adjacent to the eye muscle nuclei and in the superior cerebellar peduncle (38, 39). Some similar evidence of the distribution of afferent fibers from the eye muscles to the mesencephalic nucleus of the fifth nerve and onwards is available for the cat (65).

EFFECTS OF STRETCH

No stretch reflex has been elicited from the extraocular muscles. Pulling on the tendon of the superior oblique in decerebrate goats produced either no change or a fall in rate of discharge of about 10 per cent in single motor units or motor nerve fibers. In the same animals, a brisk discharge in motoneurons of the superior oblique followed rotation of the head, and pulling on a slip of the masseter produced a reflex contraction of its muscle fibers. Pulling on the tendon of the inferior oblique sometimes produced a small increase in the discharge in fibers of the superior oblique. No response to shocks applied to the central end of the afferent nerve trunks has been observed in the motoneurons of the fourth nerve, nor has tapping the tendon of an eye muscle had any observed effect (Whitteridge, unpublished observations). These results agree with those of McCouch & Adler (103) on the cat. Many authors have observed that the motor discharges during nystagmus and vestibular reflexes are unaffected by cocainization of the eye muscles (112) or by peripheral section of the motor nerves (105).

One can therefore conclude that a stretch reflex is probably not a basic mechanism associated with these muscles. Correspondingly, there is no increase in the discharge of afferent fibers from muscle

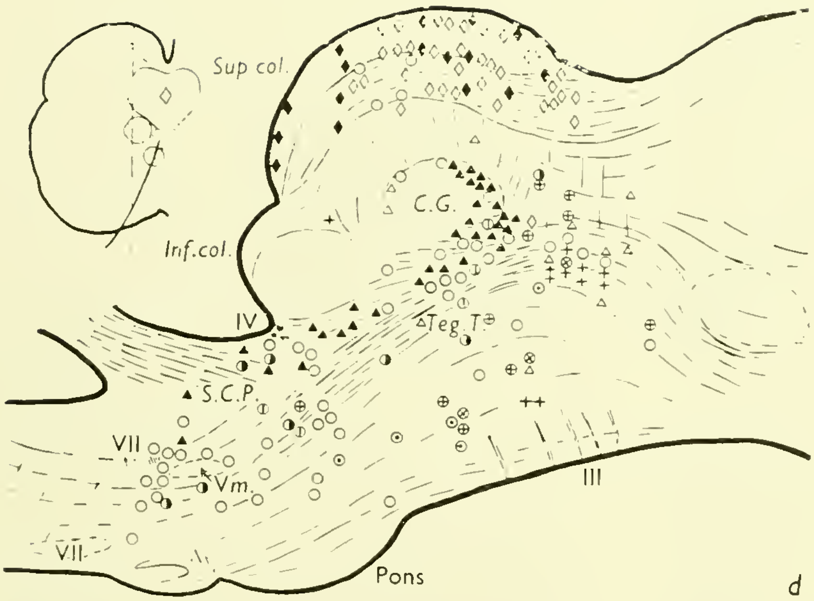

FIG. 4. Location in the goat brain of regions yielding microelectrode responses to afferent excitation from eye, jaw and limb movement, and to visual excitation. Sagittal section, 3 mm lateral to mid-line, in the plane shown on the diagram of the transverse section.

Key:

Eye-muscle responses
- ● Latency short
- ◗ Latency 20–50 msec
- ⦶ Latency 50–100 msec
- ⊕ Latency 100–180 msec
- Ƹ Repetitive
- ⊖ Inhibitory
- No latency available

Jaw-muscle responses
- ▲ Latency short
- △ Latency long

Visual responses
- ◆ To focal stimulation
- To general illumination

Limb responses +

III Nucleus and fibers of third nerve
IV Nucleus and fibers of fourth nerve
V Fibers of fifth nerve
Vm Motor nucleus of fifth nerve
VI Nucleus and fibers of sixth nerve
VII Nucleus and fibers of seventh nerve
Sup Col. Superior colliculus
Inf.Col. Inferior colliculus
C.G. Central grey matter
S.C.P. Superior cerebellar peduncle
M.L.F. Medial longitudinal fasciculus
Teg.T. Tegmental tract
P.C. Posterior commissure

[From Cooper *et al.* (37).]

spindles before the onset of vestibulo-ocular reflex movement. The first sign of movement is a discharge in the alpha motoneurons. Subsequently there is usually a decrease in discharge of the afferent fibers at the beginning of the tension increase in the muscle, and this may or may not be followed by a later increase in frequency of discharge (147). This point has so far been examined only in vestibular reflex movement, not in movement evoked from the colliculus or the cortex. If a stretch reflex does not exist, discharge in gamma motoneurons is unlikely to precede discharge in alpha motoneurons.

It has been suggested that the muscle spindles may control tonic discharge in the smaller muscle fibers of the outer surface. No difference in behavior in tonic and phasic contraction between large and small fibers has so far been observed, but further observations should be made on monkeys. It still remains possible that although the spindle does not operate a length servomechanism as it seems to do in skeletal muscle (62), it may play an important part in adversive movements initiated from stimulation of the retina (p. 1098).

VESTIBULAR REFLEXES

These reflexes have been described by Magnus (101), Fischer (66) and Lorente de Nó (97). They are usually divided into static and statokinetic reflexes, the latter being the responses produced by movement, whether rotation or linear acceleration, the former the maintained compensatory position produced by alterations in posture. The static reactions have been the object of much work in the past, but the statokinetic reactions seem to be more important and more interesting.

Reactions to Rotation in Horizontal Plane

Rotation in a horizontal plane to the right causes prompt contraction of the left lateral rectus muscle and relaxation of the medial rectus in the rabbit (51) and in the decerebrate cat. In man this reaction can be seen if fixation is prevented while the subject is rotated in a chair. Clearly the effect of this reaction is to reduce the movement of the visual axis while the body and head move. In the rabbit the ampli-

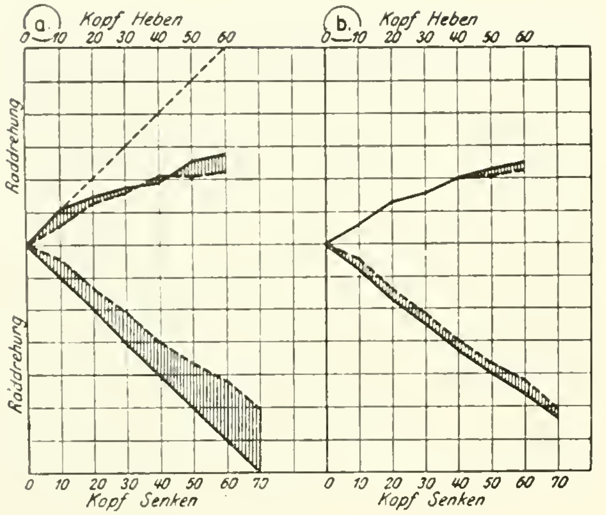

FIG. 5. *A:* Relation of head movement about a binaural axis to rotation of the eye about the visual axis in the rabbit. *Ordinates,* rotation of the eye; *abscissae,* head movement downwards *below,* and upwards *above;* in both each scale division represents 10°. The *full line* shows the effect of raising and lowering the head; the *broken line* indicates the labyrinthine effect on the eyes; thus, the *shaded area* represents the effect of the neck reflexes on the eyes. *B:* Same observations after the posterior roots of C_1 and C_2 have been cut. [From de Kleijn (50).]

tude of lateral eye movement is not greater than 20° to 30°. In the decerebrate cat, the vestibulo-ocular reflex is remarkable as the only postural reflex involving the labyrinth which is executed at about its normal speed. Rotation can evoke action potentials in the lateral rectus of up to 160 per sec. (117). The latency between the onset of movement and the first action potential can be as short as 10 to 20 msec. Further study of this point is made difficult by the latency of the vestibular endings to rotation. According to Wendt (143) the latent period in man for the slow movement of vestibular nystagmus is about 50 msec., varying with acceleration from 40 to 80 msec. For rotation in the horizontal plane, at about 30° per sec., about 60 per cent of the rotational movement is compensated. Similar extent of compensation is seen with slower movement. If a fixation point is provided, about 80 per cent of 65° head movement is compensated (143).

By injecting fluid into one semicircular canal at a time in the unanesthetized cat, Szentágothai (131) has obtained some evidence that each canal is linked chiefly to two eye muscles. For example the left lateral canal chiefly excites the left medial rectus and the opposite lateral rectus. He has anatomical evidence that these actions are mediated by three neuron arc connections through the medial longitudinal bundle. In addition there are more generalized excitatory and inhibitory connections from each canal to the other muscles, mediated by multisynaptic connections in the reticular formation. Earlier work by Lorente de Nó (98) also showed the connections with shortest latency to run in the medial longitudinal bundle, but the animals were anesthetized and the labyrinth intact and the importance of the multisynaptic connections seemed to be very much greater than the connections through the medial longitudinal bundle.

There is no maintained static labyrinthine reflex response to rotation of the head in a horizontal plane. This is attributed to the fact that no otolith organ is excited by deviations of the head in this plane. Deviations of 17° or more have been produced in the rabbit by a static neck reflex (51).

Reactions to Vertical Movement

Tilting of the head in the fore and aft plane (about a bitemporal axis) excites all four vertical canals and produces rotation about the visual axes in animals with laterally directed eyes, in fish (10), the rabbit (50) and the pigeon (11). In the rabbit this reaction consists of a rapid component and a very stable static component. According to de Kleijn (50) the horizontal meridian can be kept accurately horizontal while the rabbit head is moved through 100°, as shown in figure 5. This compensation is slightly reduced by fixation of the neck or removal of the cervical nerves. A similar static reaction is seen in fish. Here the compensation of movements of over 30° from the position of rest is not more than three quarters of the head movement. According to the graphs given by Benjamins (10), however, compensation may be perfect for the first 22.5° above and below the horizontal; he makes no comment on this point in the text.

Corresponding experiments on the pigeon gave much smaller compensation for steady displacement, the average figure being $1/12$ of the angle of tilt of the head (10). This work has recently been repeated by Sommer & Whitteridge (127) as a result of a recent paper by Merton (107) on man. The static rotation of the eye in the pigeon is in fact only a small fraction of the head rotation, but during rotation at moderate speed the eye movement in the decerebrate pigeon compensates for 60 to 70 per cent of the head movement over a range of 10°. After

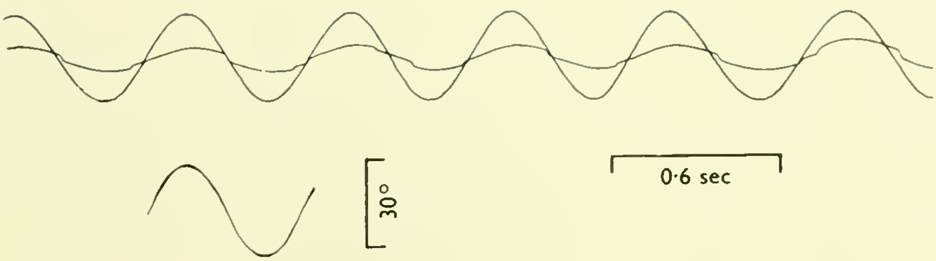

FIG. 6. Records of the excursion of the swing in which the subject is seated (*large smooth sinusoidal trace*) and of the rolling movements of the eye (*smaller broken trace*). Disregarding the irregular jerking movements, the eye moves roughly one quarter of the amplitude of the swing and lags by about 15°. In the calibration record, taken with the mica plate attached to the swing, the two traces almost superimpose, showing that the sensitivity of the two records is equal and that distortion is inappreciable at this amplitude. The calibration scale of degrees is approximate. [From Davies & Merton (49).]

rotation stops, the eye drifts back in 1 to 2 sec. or moves quickly back if a blink occurs.

It is convenient to deal here with the responses to rotation of the head about a sagittal axis in animals with forwardly directed eyes. In the decerebrate cat this produces a brisk contraction alternately in the superior and inferior oblique muscles. In man a compensatory movement was described by Mulder (108) and Breuer (21) who used the movement of afterimages against a ruler held by the teeth as a measure of the extent of compensation. These observers remark that the compensatory movements are considerable during head movement up to 30°; but that when head movement stops, the eyes drift back in the next few seconds to a displacement of $\frac{1}{8}$ to $\frac{1}{12}$ of the head movement. Unfortunately subsequent authors have only described the residual compensation (60, 66). The subject has been reinvestigated recently by Merton (49, 107). When a subject sits in a chair which swings about a ball race on a level with the subject's eye, the horizontal meridian of the eye remains nearly horizontal during rotation of up to 30° (see fig. 6). After the movement is over, the eye catches up all but about $\frac{1}{10}$ of the movement, with a time constant of about 1 sec. Visual acuity is not appreciably diminished either during the movement or during the following 2 to 3 sec. when the eye 'catches up' with the head.

If the subject lies on his back with the optical axes vertical, there is compensation during rapid rotation of the whole body in the horizontal plane; but after the movement is over, the eyes 'catch up' and there is no residual rotation. Presumably, therefore, the residual rotation present in the upright position is due to otolith activity.

If fixation is prevented, these movements are still present, but the compensation is maintained for a shorter time. The eye 'catches up' in a series of jerks. These reactions are absent in patients with bilateral destruction of the labyrinth (Merton, personal communication). Movements of the head about the sagittal axis in animals with laterally directed eyes produces contraction of the levator palpebrae superioris and the superior rectus on the lower side of the head and contraction of the inferior rectus on the upper side.

In man, the monkey and the cat which have forwardly directed eyes, nodding movements about a bitemporal axis produce contraction of both recti superiores and the levatores. In animals these reactions are brisk and their maintenance is presumably due to stimulation of the otoliths. In man, evidence of this mechanism appears in those patients who have paralysis of voluntary upward movement. If they fixate on an object in the horizontal plane, they may be able to maintain fixation in spite of forward flexion of the head on the neck. This requires contraction of the elevators of the eyeball. This may occur even when fixation by itself is ineffective, as when the patient fixates an object in the horizontal plane but is unable to follow as it is slowly moved upwards (82).

NECK REFLEXES

By the classic methods of Magnus it is possible to show that bending the neck may produce compensatory eye movements. These are clearly seen in rabbits (51). Recently McCouch *et al.* (104) showed

that these reflexes are still present after removal of the neck muscles when endings in the upper vertebral joints are still present. The neck muscles are not thereby excluded from playing some part in these reflexes; the small muscles of the neck are richly supplied with muscle spindles (Cooper, personal communication). In an experiment on man the head was kept still and the trunk was moved; the corresponding eye movement was small (67).

NYSTAGMUS

Although rotation of the head in the horizontal plane to the right produces contraction of the left lateral rectus, this contraction is not long maintained but is succeeded by a quick swing of the eye to the right, followed by deviation to the left at a rate related to the rotation, another sharp flick to the right, and so on. This is vestibular nystagmus. The obvious suggestion is that the sharp flick is induced by the approach of the eye to the limits of movement and that this is signalled by the proprioceptors of the eye muscles or by tissues of the orbit. This suggestion can be excluded. de Kleijn injected a local anesthetic into the eye muscles and found no change in the nystagmus (101). McCouch & Adler (103) were quite unable to modify a vestibular nystagmus by pulling on any of the extraocular muscles. Only the midbrain is necessary for nystagmus since it persists after section of the brain at the level of the oculomotor nucleus (101, 113). It seems, therefore, that the sharp flick is initiated by midbrain structures when the discharge in the motor nucleus has persisted at a high level for a certain time.

Vestibular nystagmus may also be produced by unilateral injury to the labyrinth, the vestibular nuclei or the cerebellum, and may be accompanied by head nystagmus. Naturally other means of exciting the labyrinth by caloric or galvanic stimuli will also cause nystagmus as long as the labyrinth is intact.

There is no doubt of the existence of a projection from the retina to the cerebellum (126, 144). Many of the responses to pulling on extraocular muscles which appeared after latencies up to 100 to 150 msec. were found in the superior cerebellar peduncle (38) and appeared to be due to a pathway through the cerebellum. Little is known as yet about possible functions of such pathways.

ADVERSIVE MOVEMENTS OF EYES

In the lower vertebrates, movements of the two eyes in response to a visual stimulus in the peripheral field may be independent. The extreme case is the chameleon, the eyes of which perform constant independent scanning movements but converge onto an interesting target.

In birds, movement of the two eyes is usually conjugate; and in mammals all normal movements of the two eyes are closely linked and consist of conjugate movements and of movements of convergence and divergence. When a stimulus—particularly a moving stimulus—falls on the peripheral retina, the eyes and often the head are moved so as to allow the image to fall on the region of greatest retinal sensitivity.

The greater the difference between acuity at the fovea or area centralis and the rest of the retina the greater the movements required to examine objects in the visual field. Thus the rabbit is believed to have fairly uniformly poor retinal sensitivity, and it makes few head movements and few adversive eye movements. The squirrel probably has very high sensitivity in its pure cone retina and again makes few head or eye movements. On the other hand, birds make very extensive head movements to bring visual images onto the fovea. 'Bird-like' movement of the head in ordinary speech means rapid movement of the head with pauses during which the head is held quite still, presumably for fixation. On the whole the larger birds show more eye movement, and the pelican, which cannot move its enormous beak suddenly, has a considerable range of eye movement. In those birds which do move their eyes freely, head movement is slower and less jerky. The jackdaw moves its eyes up to 30°, particularly, it is said, in unfamiliar surroundings. Otherwise it moves both head and eyes. The pigeon and hen both show adversive movements of about 10°. In the owl the eyes are tubular and fixed to the orbit. Here all movement is carried out by the head (121). A good comparative account of these movements is given by Bartels (9).

Adversive movements have been studied by making the visual field move and watching the movements of the head and eyes. As the field moves, the head and eyes follow over a certain range, giving a so-called pursuit movement. This is interrupted by a quick flick of the head and eyes in the opposite direction, and the pursuit movements begin again. This

phenomenon is called optokinetic, train or railway nystagmus. It has a latency of about 0.2 sec. (59). It is best elicited in lower animals by surrounding the animal with a revolving drum painted in wide vertical stripes. This is adequate in lower vertebrates (19, 122, 137) but may not be enough in dogs and especially in monkeys to attract the animal's attention. It is said that dogs will ignore rotating stripes but may follow a series of rabbits made to move past the eyes. Some believe that the response is not then due to olfactory stimuli. Although vestibular and optokinetic nystagmus use the same final common paths, their neural pathways diverge widely. In patients with complete bilateral destruction of vestibular nuclei due to treatment with antibiotics, vestibular nystagmus is abolished, whereas optokinetic nystagmus is unimpaired (29).

Rademaker & Ter Braak (113) have pointed out that the maximal acceleration of the slow (pursuit) phase of optokinetic nystagmus is $10' \cdot sec.^{-2}$ whereas the slow phase of vestibular nystagmus may start with an acceleration of $120° \cdot sec.^{-2}$. Optokinetic nystagmus will be discussed further in connection with the cortical pathways involved.

SUPERIOR COLLICULUS

Anatomy

Although it has long been known that the superior colliculi (anterior corpora quadrigemina) and their homologues form the principal center for vision in the lower vertebrates, they are so overshadowed by the increasing importance of the occipital cortex in mammals and especially in primates that very little attention has been paid to them, and even textbooks of ophthalmology almost ignore them. The work of Apter (5, 6) on the cat has led to considerable activity in this field in the last 10 years.

Detailed accounts of the fine structure of the superior colliculus in all classes of vertebrates are given by Ramón y Cajal (115) and of the optic lobe in birds by P. Ramón y Cajal (114). Descriptions of its afferent and efferent fibers have been given by Huber & Crosby (85–87) for lower vertebrates and by Crosby & Henderson (46) for mammals. The stratification of the cells and fibers of the colliculus is very striking in many species, and there are large differences in the cholinesterase content of different layers. The colliculus is one of the richer sources of cholinesterase and cholinacetylase (76).

In mammals the afferent tracts from the retina and from the occipital cortex enter the colliculus in the stratum opticum. Many terminal fibers turn superficially to end in the stratum griseum superficiale. Cells in this layer send fibers to the stratum griseum profundum perpendicularly to the surface, crossing the stratum opticum. Impulses may spread transversely by the most superficial layer, the stratum zonale. The deepest layers of the stratum griseum profundum contain large cells the axons of which form the colliculo-oculomotor pathways and the tectospinal tract. The colliculus receives somatic fibers from the medial lemniscus and the fifth nerve system, and also fibers probably from the vestibular apparatus via the inferior colliculus (73). There is good evidence for a projection from the colliculus to the cerebellum (126).

The histological evidence for a projection of separate quadrants of the retina on to separate areas of the superior colliculus is strong, although the Marchi method does not permit degenerated fibers to be followed to their terminations. Histological studies have been made on fish (2, 90, 99) and, among mammals, on the rat (94), rabbit (23), cat (8) and opossum (17). Brouwer & Zeeman (23) have tried to trace fibers from monkey retina to the colliculus; and although they obtained some degenerated fibers from lesions in the periphery of the retina, they failed to observe any degeneration after lesions limited to the macula and concluded that there are no direct macular fibers.

Electrophysiological Studies

Earlier observations on potential changes in the superior colliculus were made with illumination of the whole eye or electrical stimulation of the optic nerve (142), but Apter (5) obtained good localization of potentials in the cat colliculus with a light subtending 4.5° at the eye. Similar evidence of localization has been obtained by Buser & Dusardier (27) in fish, by Gaze (71) in the frog (fig. 7), Hamdi & Whitteridge (74) in the pigeon, rabbit and goat, and by Daniel & Whitteridge (unpublished observations) in the monkey. In the monkey it was difficult to obtain responses from the peripheral field whereas responses within 10° of the macula were easily obtained. In view of Brouwer & Zeeman's difficulty in finding degenerate fibers (23), these physiological responses may be caused by fibers which have been relayed, perhaps in the lateral geniculate body. In

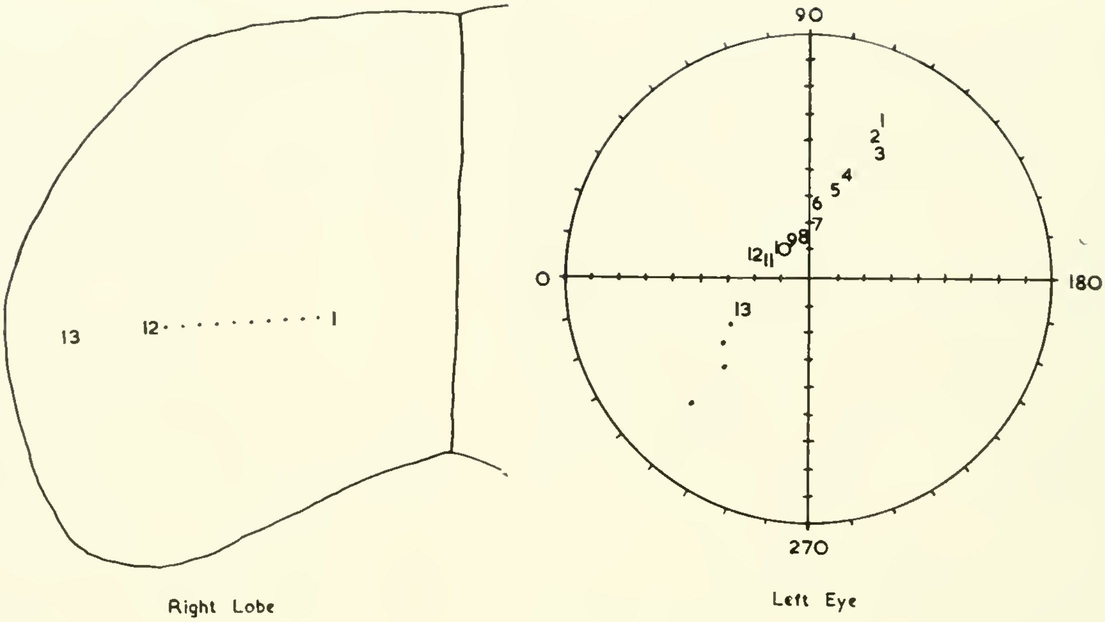

FIG. 7. Localization of the visual field in the optic lobe of the frog. *Right:* Perimeter chart for the left eye in which figures *1* to *13* represent the different positions of the stimulus light flashes required for maximal response, as the recording microelectrode was moved in orderly steps of 0.1 mm across the surface of the contralateral (right) optic lobe. The positions of insertion of the electrode are shown in the *left diagram* which gives the outline of the lobe. At *insertion 13*, the electrode was lowered through the substance of the lobe. As the electrode penetrated, the optimum position of the stimulus light moved downwards and outwards. This is to be expected since the surface of the lobe curls around underneath at the lateral edge, and apparently some of the superior retinal area is represented here. [From Gaze (72).]

all cases the upper visual field is represented nearer the mid-line of the superior colliculus, the lower field more laterally. The horizontal meridian is shown by some workers as running backwards and medially, by others as running parallel to the mid-line. This arrangement of the projection is the same for animals with frontally and with laterally directed eyes, but animals with laterally directed eyes, such as the rabbit, have almost entirely contralateral representation while the cat has bilateral representation. In the cat the anterior pole of the colliculus is devoted to the area centralis of the retina which seems to have a larger central projection area than the rest of the retina (5).

Effects of Stimulation and of Lesions

There is no doubt that stimulation of the superior colliculus in some mammals can cause adversive eye movement. This has been shown for the cat with implanted electrodes in the conscious animal (fig. 8) (79) and by using strychnine with very light anesthesia (6). No experimental data are available for the monkey or man.

There is also good evidence that pursuit movement induced by stripes on a rotating drum can be abolished by destruction of the superior colliculus in the guinea pig (125) and in the cat (122, 123). How much importance this 'subcortical' optokinetic mechanism has in man is quite unknown. On the basis of observations on the guinea pig, it seems to be assumed by Carmichael *et al.* (29) to exist in man. Rademaker & Ter Braak (113) suggest that weak stimuli set up a cortical optokinetic nystagmus, whereas large stripes may actuate a subcortical mechanism. This distinction seems to have some experimental basis. There is no doubt that the direct visual connections to the superior colliculus become smaller and less important in man, and corticocollicular connections from area 19 become much more important (44, 111). Certainly no signs of subcortical optokinetic movements are seen in blindness

from cortical lesions in man, but persistence of optokinetic nystagmus has been claimed in coma, in the newborn and in 'extreme idiocy.' The weight of evidence supports the view that the occipital cortex plays an essential part in all forms of optokinetic nystagmus in man.

It was said by Ferrier & Turner that eye movements are still possible after bilateral destruction of the superior colliculi in monkeys (64). This paper seems to be quoted oftener than it is read. However, in order to approach the colliculi, the left occipital lobe was removed in these experiments so that the animals were hemianopic. The only information given is that there was no ophthalmoplegia and eye movements were normal. Whether adversive movements or optokinetic movements to the left were still normal is not related. In similar experiments on cats by Spiegel & Scala (128), the occipital lobes were pushed up out of the way. They may have been damaged and their excitability was certainly lost. No tests of optokinetic nystagmus were made. There is no doubt that a pathway from the frontal area to the nuclei of motor nerves of the eye exists which does not pass through the colliculi (47).

In man the presence of supranuclear palsies from pressure on the tectum (Parinaud's syndrome) is most easily explained as interference with the superior colliculi. The representation of the upper quadrants at the anterior medial parts of each colliculus would account for the frequency of paralysis of upward movement. A nuclear ophthalmoplegia could be due to pressure and distortion of the midbrain extending more deeply to the third nerve nucleus. How such a lesion would affect fibers from the frontal lobes is not clear.

In the lower mammals the colliculus plays a large part in adversive movements; in monkeys and man it is at least a distribution center for descending pathways for eye movement.

Proprioceptors

It has been remarked by Cooper *et al.* (40) that units stimulated by pulling on the external extraocular muscles in the goat were to be found only in the deeper layers—stratum griseum profundum—in the colliculus (see fig. 4). One may therefore speculate that whether a particular visual stimulus in the peripheral field gives rise to an eye movement, or both head and eye movement, may depend on proprioceptive impulses signalling the initial relation of the eye to the head.

FIG. 8. Adversive movements in the unanesthetized cat following stimulation of the left superior colliculus. [From Hess (80).]

EYE MOVEMENTS AND VISUAL CORTEX

Stimulation of the visual cortex produces eye movements in the lightly anesthetized monkey (25, 46). Stimulation further forward on the lateral surface of the hemisphere also gives eye movements, but the directions of the responses are reversed. Whereas stimulation of the upper part of area 17 evokes downward movement of the eyes, and vice versa, stimulation of the upper part of area 19 causes upward movement. This may agree with the supposed homology between area 18 and 19 and the second—mirror image—visual area seen in the lower mammals, such as in the rabbit (134).

Fibers from areas 18 and 19 have been traced by Crosby & Henderson (46) as the occipitocollicular bundle in the macaque. This crosses the pulvinar and runs back adjacent to the posterior commissure to enter the superior colliculus as the deep layer of the stratum opticum.

The simplest picture of the process of fixation would be that impulses from the peripheral field of the retina reach area 17 and from there, or from the areas just anterior, give rise to impulses which run

to the superior colliculus and from there are distributed to the oculomotor nuclei.

In support of such a scheme one can cite the rather rare patients with bilateral damage to the peristriate region who have a spasm of fixation whereby they have great difficulty in transferring their point of fixation once they have visually grasped a particular object. Such a patient was described by Holmes (83) and the symptom may form part of Balint's syndrome (77). Here the mechanism just described is presumably intact but cannot be inhibited readily in order to transfer gaze to other targets. Even more rare are patients in whom the occipital visual centers are intact, and there is no visual defect, but who find it impossible to maintain fixation steadily even though the eyes can be moved to command. It is suggested that the lesion interrupts the occipitocollicular fibers as they run through the pulvinar (83).

It is also tempting to think of the frontal eye field as an area concerned with 'voluntary' eye movements, i.e. with movements of the eyes on command and the initiation of large scale scanning movements. In a very clear analysis Graham Brown (25) divided this area into two, an upper in which stimulation gives rise to movement of the head without movement of the eyeballs relative to the head. If, however, the head is restrained, the eyes then move in their sockets. Stimulation of the lower area gives movement of the eyes to the opposite side and little or no movement of the head.

Carmichael *et al.* (27) believe that lesions of the angular and supramarginal gyri impair optokinetic nystagmus, and Henderson & Crosby (78) find an inhibitory effect on optokinetic nystagmus exerted by the frontal eyefield. They agree that areas 18 and 19 must be intact for optokinetic nystagmus to appear. The frontal area has been reinvestigated recently by Crosby *et al.* (47) in the macaque. These authors have obtained an orderly series of eye movements on stimulating sites in the frontal lobe regularly located along two loci at right angles to each other. Apart from providing yet more evidence of topological organization in the central nervous system, this observation is unusually difficult to interpret.

It is, however, rather surprising that the frontal lobe is included with the occipital by Fox & Holmes (66) as areas in which lesions can impair optokinetic nystagmus.

SUBSIDIARY CENTERS OF GAZE

It has been claimed that there are two subsidiary centers for eye movement, one the lateral center for gaze in the pons located in or near the para-abducens nucleus (82), the other for vertical movements in or below the superior colliculus. The strongest evidence for the center for lateral movements is that lesions in this part of the pons have caused bilateral supranuclear palsy of adversive movements both of the lateral and of the medial recti. Adversive movements of medial recti are impaired but convergence movements are unaffected. It has therefore been assumed that cortical fibers descend to this nucleus and that fibers from it run to both abducens nuclei and to the medial rectus via the posterior longitudinal bundle. There are others who consider the suggestion of a pontine center for gaze an unprofitable hypothesis (3, 32), and it is doubtful if any center for vertical movement need be postulated other than the layers of the superior colliculus.

EYE MOVEMENT IN MAN

Fixation Movements

Eye movement has been intensively studied by photographic methods for the last 50 years (57, 58, 96). Recently the movements during fixation have been examined by means of reflection from a drop of mercury on the cornea (7), from a contact lens (53, 56, 119, 120), and most recently from a mirror carried on a stalk from a contact lens (55) and a light cup (88). All authors agree that during fixation there is *a*) a continuous tremor with amplitude of 4 to 6″ at 30 to 50 cps, *b*) irregular flicks of 5 to 60′ at irregular intervals and *c*) a slow drift of about 1′ per sec. The tremor seems to be due to irregularity of excitation of the extraocular muscles which receive a heavy tonic discharge at rates in each unit well below fusion frequency (13). During attempted fixation, flicks and drift seem to be random so that the image travels around the central area of the fovea 100 μ diameter. As the image approaches the edge of this area (see fig. 9), it is found that the likelihood increases that the next flick will move the image back to the center of the fovea (53).

The effect of these movements is to move the edge of the visual image across the cones of the fovea. This constant movement opposes the adaptation of

the receptor mechanism. If the image is stabilized, which can be accomplished by viewing light which has been reflected from a contact lens, so that it moves with eye movement, then the visual detail seen rapidly decreases, and contrast in the visual field disappears after some seconds, abruptly reappears and again proceeds to fade (55). It was thought that elimination of 95 per cent of the movement of the target relative to the retina would provide adequate fixation. In fact stabilization has to be much better than this, and an increase in stabilization from 99.94 per cent to 99.96 per cent results in a large change in visibility (54).

Very fast movement of the visual field diminishes contrast, since for any unit visibility depends on the product of light intensity and time of exposure. For total exposures less than about 0.1 sec., movement of the image reduces visibility (116); however, for exposures lasting over 0.2 sec., movement of the image greatly increases visibility. Vibration of small amplitude at 16 cps greatly reduces visibility (109).

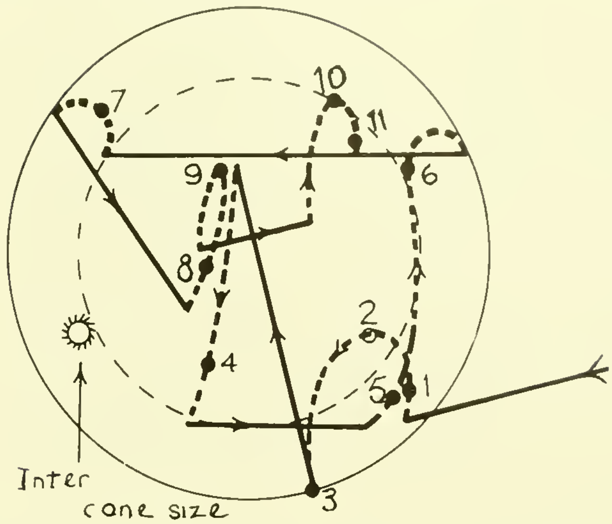

FIG. 9. Movements of a retinal image indicated by alternating *continuous* and *interrupted lines*. The diameter of the circular retinal area is about half that of the 'central territory.' The tremor movement which has been omitted has a median excursus of about 1.3 min. of arc or 6 μ. [From Ditchburn (54).]

Saccadic and Pursuit Movements

During reading or scanning of the visual field, the eyes are moved in brief jerks or 'saccades' (30, 138) (see fig. 10). The velocity of movement is constant for a particular amplitude of movement for any one subject and cannot be altered voluntarily. It increases somewhat with increasing amplitude of movement. The range for normal subjects is about 200 to 400° per sec. (22, 26, 137). When the eyes are moved from one target to another, there is usually a slow drift or possibly a flick after the rapid movement is over. The drift and flick may be in the same direction of movement or in the opposite (56). Apparently the eyes carry out a 'preset' movement of approximately the correct amplitude and bring the fixation target to the fovea by the final drift or flick. There is no evidence of check movements of antagonists to stop the movement. In reading continuous lines of print, saccadic movements last about 20 to 50 msec. Each is separated by a fixation pause of about 0.3 sec. The frequency of movements is variable and in reading regression movements frequently occur. During a normal line of 4½ in. a skilled reader will make about six fixation pauses depending on the difficulty and on the interest in the material read (138).

In addition to saccadic movements, it is also possible to make smooth pursuit movements. If an observer is set to follow a spot which is performing simple harmonic motion, his eye movements change progressively, as shown in figure 11. He at first attempts to follow by a series of vertical or horizontal movements at irregular intervals—'positional correction.' After a few repetitions, he follows by movement of the eye at uniform velocity and approximately correct direction with corrective movements—'velocity control.' Finally by altering the velocity of

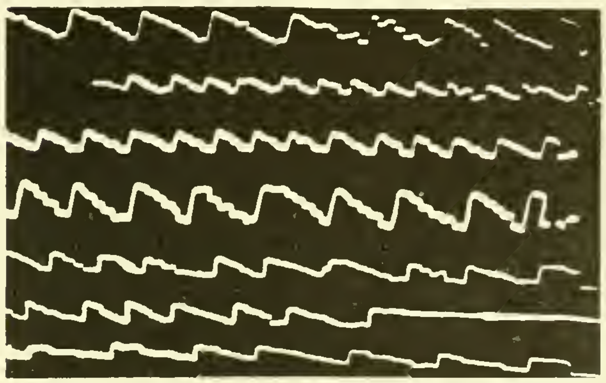

FIG. 10. Saccadic movements recorded by the corneal reflection method. Records made by a number of different subjects. [From Carmichael & Dearborn (30).]

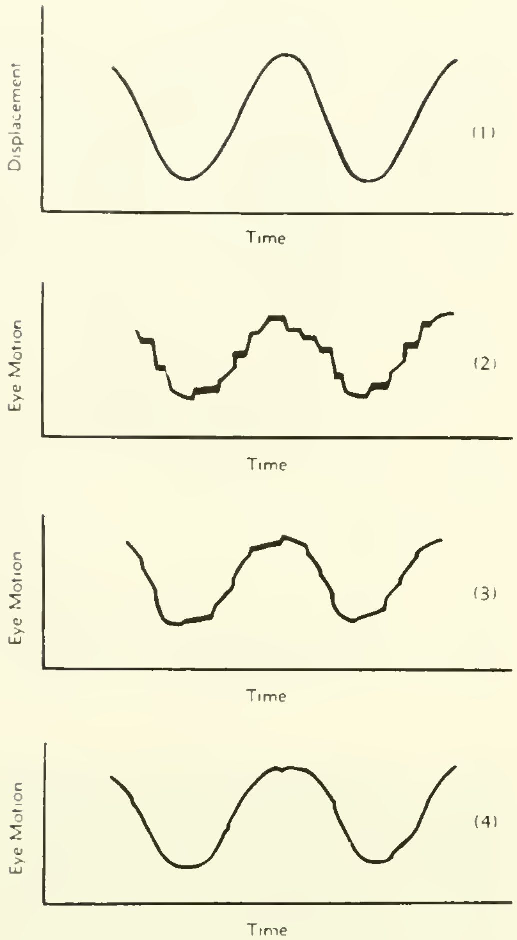

FIG. 11. The improvement in following movements made by the human eye in following a target moving sinusoidally. (*1*) Acutal motion of the target. (*2*) First solution of tracking problem. (*3*) Second (velocity) solution of tracking problem. (*4*) Third (acceleration and velocity) solution. [From Stroud (130).]

movements the subject gets very close to simple harmonic movement of the eyes (130). This rapid improvement with practice was also observed by Dodge in 1907 (58) who watched subjects following the movements of a pendulum. He pointed out that if the pendulum is obscured for part of its course, the eye lags and makes large saccades to catch up as the pendulum reappears. Similar behavior is observed in all tasks where the eyes must follow a moving target. At first the eyes lag by at least the reaction time of about 0.2 sec., or nearer 0.5 sec. if the stimulus falls at first on the peripheral field. If the target movement is regularly repeated, its movement is rapidly learned and the lag between eye movement and target movement disappears. At this stage eye movement becomes a special case of the problem of the human being as an operator in a servo system, and the general principles described by Craik (44) apply. The subject makes periodic attempts to reduce the error between target and fixation point, and any procedure tried out and found to minimize this error, be it positional change, steady movement or velocity change, is continued until further errors accumulate.

Integration of Eye Movements

It is remarkable that there is no coherent view on the relation between reflex mechanisms originating in the neck, labyrinth and eyes, which act on the eye muscles. As far as the neck and labyrinth are concerned, algebraic summation of their effects has been suggested by Magnus. The relation of cortical mechanisms to subcortical postural mechanisms is much more obscure. It is generally held that the labyrinthine mechanisms are of little importance in the monkey and in man, and that cortical mechanisms are so much more important that they can completely compensate for the absence of those of labyrinthine origin. In body posture control, Bieber & Fulton (12) have suggested that vestibular mechanisms are inh bited by the cortex normally and that only after removal of the motor and premotor cortex do vestibular attitudes appear in the monkey. There seems to be much more to be said for an alternative view that eye movements are controlled at a series of levels in the central nervous system in the Jacksonian sense, but that at each level some degree of stabilization is attained, a degree of stabilization which is essential if the commands of the next higher level are to be effectively carried out.

After complete destruction of the vestibular apparatus, there may be a considerable degree of cortical compensation, especially in young subjects, but the reaction to sudden passive movement is seriously and permanently defective. Some patients, in whom the vestibular fibers of the eighth nerve were bilaterally destroyed by Dandy, complained that their vision was 'jumbled' while they were pushed over rough ground in a wheel chair, although at rest vision was perfectly normal. While being pushed along a hospital corridor they were unable to recognise the faces of friends (68). In the history of a patient who apparently developed bilateral and isolated degeneration of the vestibular nuclei, one of the earlier symptoms was difficulty in driving a car

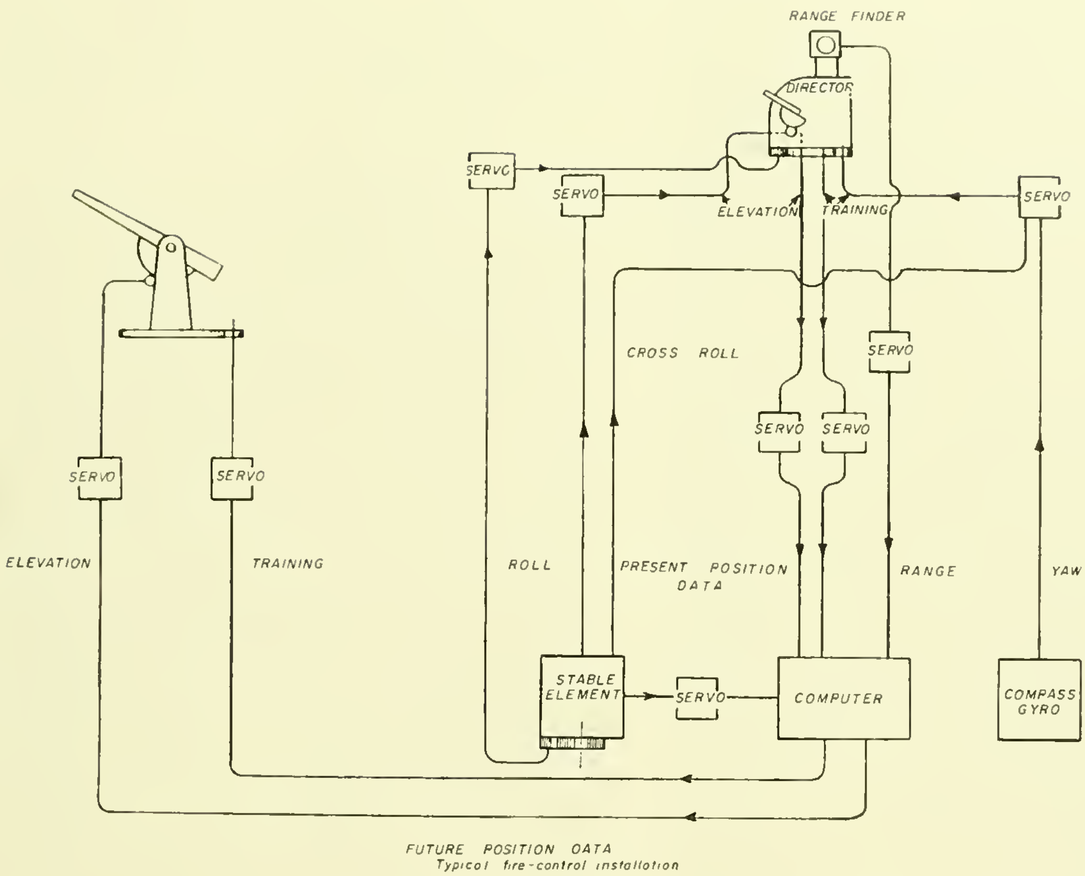

FIG. 12. A naval stable platform for a fire control installation. The observer using the range finder and the director are on a platform which is stabilized against roll and change of course (yaw). [From Gairdner (70).]

which nearly led to accidents and forced the patient to give up driving (95). In a description of his life since he became deaf at the age of 15, a patient of 50 remarked on the movement of his field of view with his head and added that "though this disability has become modified with the passage of time, it is still obvious when in a vehicle bumping over bad roads." His illness was cerebrospinal meningitis apparently with complete destruction of the vestibular apparatus (4).

In view of this unequivocal history extending over 35 years, one may perhaps cautiously differ from Holmes who holds that vestibular mechanisms are of little importance in ocular disturbances since symptoms of this type are not permanent (83). If the lesions are complete, their effects are in fact permanent.

The existence of labyrinthine effects on the eyes in man is firmly established in the case of rotation about an anteroposterior axis, a movement which cannot be carried out to order. The fact that the movements of labyrinthine nystagmus may begin with a latency of 50 msec. or thereabouts, whereas those of optokinetic nystagmus have a latency of over 200 msec., is further evidence for the existence of labyrinthine reflexes in normal subjects.

At this point the analogy from fire control in a battleship is useful (see fig. 12). The platform which carries telescopes for spotting naval or aerial targets has to be stabilized against roll and change of course and pitch, if that is a serious problem. "No one can track with hand-operated telescopes specks in the sky from a platform rolling erratically and unpredictably" (70). Once the platform is stabilized, it is easy to keep the target in the field of view of a telescope and by fine adjustments of the telescope mounting to keep the target upon cross wires. In the same way, if the head and the eyes are stabilized against

movement of the body, it is possible for the fixation reflex to operate to keep the target on the fovea.

When the stabilization by the labyrinth breaks down, as in side-to-side movements of the head faster than 2 per sec., then the visual field will appear to move and visual acuity goes down. The same arguments concerning stabilization at each level may be applied to the cortical control of eye movement. The occipital cortex, occipitocollicular tract and superior colliculus form a system by which an image of a point in the periphery is brought to the fovea and held there. If the image wanders off the fovea, appropriate corrective eye movements return it to the fovea again. Very rarely, this mechanism can be interrupted without cortical blindness by lesions of the occipitocollicular tract in the pulvinar (83). The patient then can move his eyes to command but cannot retain 'visual grasp' of objects.

On the other hand the fixation mechanism can be inhibited by turning the attention to other objects or as a result of voluntary movement of the eyes. This requires the activity of the parietal region and probably of the frontal eye field. In lesions of these areas the patient is able to fixate on an object but has great difficulty in 'letting go' of it and may have to blink to change his fixation point. The highest center must be able to enhance or inhibit the activity of subcortical reflexes, as Graham Brown most clearly pointed out; in order that both head and eyes may be moved to the side, the upper frontal area for eye movement must be able to inhibit the subcortical orientation reflex which would otherwise keep the visual areas fixed in space while the head turns. The relation of the cerebellum to these levels of organization of eye movement is still a subject for speculation. The existence of cerebellar nystagmus is denied by some but affirmed by Holmes (84) who holds that it is exaggerated during attempted fixation whereas vestibular nystagmus is more marked when fixation is made impossible. de Kleijn & Magnus (52) showed that righting reflexes persisted after destruction of the cerebellum. Unfortunately, this was distorted by textbook writers into the statement that the cerebellum has nothing to do with postural reflexes. Rademaker (112) pointed out that movements controlled by midbrain mechanisms were poorly executed after lesions of the cerebellum and that its 'regulating' function applied as much to movements mediated by the midbrain as by the cortex.

Evidence is accumulating that the precise performance of vestibulo-ocular reflexes requires cerebellar assistance, and there is little doubt that voluntary movement of the eyes also requires cerebellar cooperation.

Proprioceptors and Sensation

Since von Helmholtz (139) it has been realized that we have some knowledge of the position of the eye relative to the head. This can be shown dramatically by wearing a 12° prism in front of one eye with the other eye closed. If the hand is brought quickly from behind the back to grasp at an object in the visual field, the subject's hand misses the target by nearly 25 cm. If, however, the hand is brought up slowly, then the movements are corrected and the target is attained. If, after wearing the prism for some minutes, the subject removes it and repeats the attempt to grasp an object, he now misses by an equal distance on the other side. It is not difficult to show that this knowledge of the direction of the visual axis is unaffected even if the subject can not see his own nose or cheek. The judgments of 'subjective horizontal' and 'subjective mid-line' have long been thought to depend on the activity of the eye muscles, and there has been much controversy on the reliability of these judgments. Bourdon (19) found subjects could be consistent to 1.5° on the horizontal and the mid-line, but there is considerable variation between subjects. Ludvigh (100) states that errors up to 6° may be made but Walsh (unpublished observations) found this is an outside figure as the standard deviation is 3 to 4°.

Clearly then we have some knowledge of the direction of the visual axis. What is not clear is whether this is due to knowledge of the number of motor impulses reaching the eye muscles—the 'outflow theory'—or some knowledge of the afferent impulses arising in the proprioceptors of the eye muscles—the 'inflow theory.'

Sherrington (124) observed that three points arranged vertically do not appear to tilt when observed in tertiary positions of the eyes. The images of these points must be on retinal points forming an angle with those originally stimulated, and he concluded that the new interpretation implied that some information about the rotation of the eyeball was available to the brain and was derived from proprioceptors. It is noteworthy that Sherrington's situation is one in which the observer is called on to make a perfectly familiar judgment in which the position of the eyeball is an essential feature. It is not

possible to dismiss this observation as contaminated by ideas of verticality from the edges of the projection area, since afterimages of three vertical points observed in the primary position do appear tilted when the eye moves to a tertiary position.

Sherrington's interpretation however has not been generally accepted. Most ophthalmologists have followed von Helmholtz who wrote at a time when proprioceptive mechanisms were not understood, and the longstanding confusion over their existence in the eye muscles strengthened the belief that proprioceptors were unnecessary.

It is quite clear that we have little or no direct conscious knowledge of the movements of our eyes. The most striking evidence is the surprise which greeted the first observations of saccadic movement in reading, movements of which the subject is completely unaware. The knowledge that the eye movement is jerky is irrelevant to perception in reading.

It has long been reported that an attempt to move the eye by means of a paralyzed muscle, for example attempting to move the right eye to the right with paralysis of the right lateral rectus muscle, results in apparent displacement of the visual field to the right. The objection that the covered normal eye has made a movement can be met by studying patients with one eye completely immobile and with paralysis of one muscle of the other (89). Attempts to move the eye in the direction of its paralyzed muscle still give rise to apparent movement of the visual field. The same results follow attempts to move the eyes after paralyzing or weakening the muscles with cocaine (92) or tubocurarine (75; Walsh, unpublished observations).

These experiments support the outflow theory rather than the inflow theory. It is not unreasonable to suggest that, when we start a voluntary movement, we expect the visual field to change in accordance with the eye movement and prepare to interpret the retinal data accordingly. Sherrington's arguments for 'inflow' can perhaps be interpreted in terms of monitoring of the outflow to the muscles in the tertiary positions of the eyeball. Others who have ascribed some importance to the eye muscles in judgment of visual space, e.g. Tschermak and his pupils, have used the phrase 'myosensory tension' and have avoided taking sides in the controversy (140).

The proprioceptors in the eye muscles then cannot be shown to play any part in the conscious appreciation of eye movement and do not seem to be responsible for any form of stretch reflex. They may modify adversive movements initiated by retinal stimuli, and the muscle spindles in man, one may speculate, may play a part in maintaining fixation or at least in signaling the eye movements in fixation

One possible role for muscle spindles, i.e. endings the sensitivity of which can be changed by the central nervous system by altering the gamma efferent discharge to the intrafusal muscle fibers, is to signal small movements when a target is being fixated. It is possible that the discharge to the intrafusal fibers is increased whenever fixation occurs. In this way the sensitivity of the spindles could be increased at any point in the whole range of movements available to the eyeball. Such a mechanism would be more sensitive for the detection of small movements than for signaling the position of the eyeball relative to the head. In the goat the eye muscles can probably signal a movement of 0.5° per sec. (36). This is approximately the minimal movement which can be detected by the human eye without a fixation point (19). The sensitivity of detection of eye movements should be as great as this, since to be sure that a target has moved upwards on a blank field, one must be sure that the eye has not moved down.

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The neural control of respiration

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CHAPTER CONTENTS

THE EXPRESSION 'RESPIRATION,' as used in this section, refers only to external respiration, in particular to the nervous control of the respiratory muscles. Because of the incorporation of the gas-exchange surfaces within the body, the activity of these muscles must be a rhythmic one; for functional reasons it must be autonomous. Furthermore, pulmonary ventilation—the result and measure of respiratory activity—must be, through chemical or nervous reflex mechanisms, continually adapted to the needs of the body. The protection of the respiratory organs is also mediated through special nervous mechanisms, and the establishment of contact between individuals through the medium of speech requires some means of cortical control of respiration. In connection with the manifold functions which respiration subserves, various questions arise as to the position of the respiratory centers, the causes and mechanisms of their automatic rhythmicity, and the possibility of nervously coordinated adaptive processes.

In 1812 the respiratory center was located for the first time in the medulla oblongata by Legallois (121, 122). His experiments were repeated by Flourens (66, 67) who located the respiratory center in a narrowly circumscribed area at the level of the calamus scriptorius of the medulla oblongata, in the so-called *noeud vital*. But various attempts to confirm these assertions led, already in the nineteenth century, to the discovery of additional spinal, pontine, mesencephalic and diencephalic, as well as cortical, nervous structures which also participate in respiratory regulation. Today it is customary to separate a primary respiratory center in the reticular substance of the medulla and pons from the superimposed or secondary respiratory centers in the mesencephalon and diencephalon, as also from the spinal effector centers in the spinal cord.

An adaptation of respiration to changing bodily needs can result through a change in the frequency of respiration, a change in the respiratory amplitude, or through both changes occurring concurrently. Considered from a neurophysiological point of view, as well as in regard to energy expenditure, the means through which the adaptation occurs is by no means a matter of indifference. Therefore, in the following, we shall attempt to avoid using the customary clinical expressions 'respiratory activation,' and 'respiratory inhibition,' substituting therefore the somewhat more

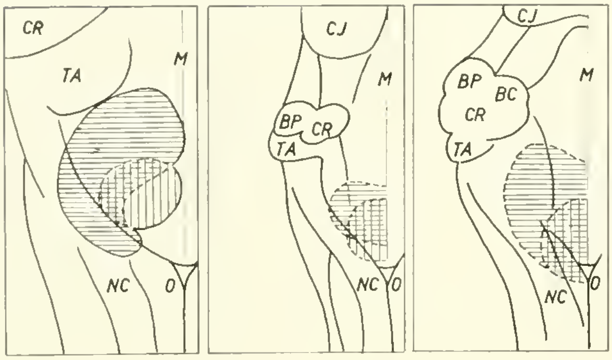

FIG. 1. Regions of the right half of the brain stem, stimulation of which influences respiration, shown as projected on the floor of the fourth ventricle after removal of the cerebellum. *Vertical lining* indicates areas giving inspiratory responses; *horizontal lining*, expiratory responses. *Left:* Lower brain stem of *Macaca mulatta*. [From Beaton & Magoun (18).] *Middle:* Brain stem of the cat, extending further cephalically than the left figure. [From Pitts *et al.* (156).] *Right:* Same region of the sheep. [From Amoroso *et al.* (7).] *BC*, brachium conjunctivum; *BP*, brachium pontis; *CJ*, inferior colliculus; *CR*, restiform body; *M*, mid-line; *NC*, cuneate nucleus; *O*, obex; *TA*, acoustic tubercule.

detailed expressions 'increase or decrease of the respiratory frequency or of the respiratory amplitude' and 'displacement of the respiratory middle position toward the inspiratory or the expiratory side,' in order to characterize a reaction.

ANATOMICAL LOCALIZATION OF RESPIRATORY CENTERS

Primary Respiratory Centers in the Medulla Oblongata

Investigations in the medullary region and in the upper spinal cord, by means of transverse and longitudinal sectioning, have led to the assumption of a paired respiratory center in the medulla. The results of central stimulation indicate two half-centers on each side, an inspiratory and an expiratory. Both are localized in the reticular substance and appear not to be sharply separated from one another. Nevertheless, in the cat (12, 156), monkey (18) and sheep (7), the anatomical substrate responsible for inspiratory activity is predominantly assigned to the medial reticular substance and the medial part of the lateral reticular substance. Expiratory activity, on the other hand, is localized in the dorsal and lateral stretches of the lateral reticular substance (fig. 1). One should, of course, mention that these results are based primarily on experiments involving the stimulation (or elimination) of certain regions, in which generally either high frequencies or high intensities were used and, as a rule, only strong respiratory influences were evaluated. Furthermore, not all experimental results are in agreement with the above findings. For example, Brookhart (30) was unable in the dog to separate two zones which could be demonstrated to yield functionally different (i.e. primarily inspiratory or expiratory) respiratory reactions to stimulation. In addition, action current measurements from cell elements in the medulla which discharge synchronously with respiration have only partially confirmed the results of the stimulation experiments (1, 56, 77, 189). On the other hand, in support of a separation of cell regions active in inspiration and expiration may be mentioned the separate relay centers for vagal inspiratory and expiratory reflexes, which will be discussed in the third section of this chapter.

To the respiratory substrate in the medulla must be ascribed the capability of automatic, i.e. autorhythmic, activity. In the intact organism a regulation through superimposed pontine to diencephalic, occasionally also cortical, 'respiratory centers' can be regarded as certain. But the bulbar respiratory centers represent, according to our present knowledge, the minimal substrate with which a regulated respiratory activity can be maintained and, under appropriate circumstances, react to carbon dioxide stimulation or other peripheral influences (182, 183).

Primary Respiratory Centers in the Pons

Transverse sectioning in the region between the quadrigeminal plate and the striae acusticae of the medulla oblongata lead in the rabbit (33, 130, 131), the cat (27, 126, 183) and the dog (101, 102, 127) to respiratory changes which vary according to the location of the section. After decerebration between the corpora quadrigemina, spontaneous respiration is hardly changed. Sectioning of the brain stem immediately behind the inferior colliculi also fails to produce respiratory changes, provided the cranial regions of the pons remain intact. In animals with intact vagus nerves, spontaneous respiration is only slightly changed when the section is made so as to remove the cranial third of the pons. When, in addition, the vagus nerves are cut, long periods of respiratory arrest in inspiration occur which can last several minutes. Moreover, maximal inspiratory depths are reached, so that this form of respiration has been characterized as convulsive respiration (131) or as apneustic respiration (126). The inspiratory pauses are followed by more or

less lengthy expirations. Respiratory frequency and minute volume are greatly reduced as a result. One continues to observe this apneustic respiration even when only the most caudal segments of the pons remain intact. On the other hand, an incision below the striae acusticae, separating the medulla oblongata entirely from the pons, brings about the disappearance of the apneustic respiration. The medullary animal then shows either eupneic respiration, to be sure not always well coordinated, or very deep breaths in regular succession. The latter respiratory form has been described as 'gasping' respiration (126). In many cases transverse sectioning in the upper and lower regions of the pons leads to periodic respiration (102), so that an apneusis is not always observed.

These ablation experiments have led to the assumption of two pontine respiratory centers. In the cranial part of the tegmentum pontis lies a nervous substrate inhibiting respiratory activity, which is called the pneumotaxic center. A more extensive region in the middle and caudal pons is called the apneustic center. The latter exerts a strong tonic effect on the bulbar inspiratory center and, therefore, apneustic respiration results when the inhibiting expiratory influence of the pneumotaxic center is abolished. In conformity with stimulation and coagulation experiments in the pontine tectum (16, 105), the locus coeruleus may be assumed to represent the bilaterally situated pneumotaxic center. Its isolated bilateral destruction in the vagotomized cat results in apneusis. In man destruction of these nuclei leads to a severe cerebral dyspnea with large, inspiratorily emphasized respiration, or with periodic respiration (87). Concerning the location of the apneustic center uniform accounts are, up to the present, not available. Presumably it includes extensive areas of the lateral reticular substance of the pons (139).

Structures of Higher Brain Stem Involved in Respiratory Regulation

It was recognized early in the course of investigation of nervous centers that faradic stimulation of the quadrigeminal plate in the rabbit produced an inspiratory displacement of the respiratory middle position, a restriction of the amplitude on the expiratory side, and a marked increase in frequency—with stronger stimulation showing concomitantly a marked motor effect (132). Inspiratory reactions were particularly easy to obtain from the caudal regions of the thalamus situated close to the third ventricle (40). Stimulation in the superior colliculi was more likely to produce an expiratory effect with a decrease in respiratory frequency and a lengthening of the duration of expiration (41). However, a subdivision in this region into zones activating respiration and those inhibiting respiration resulted first from the systematic electrical probing in the anesthetized and unanesthetized cat (90, 91, 160); the results of this appear in figure 2.

In the region of the posterior commissure, electrical stimulation causes an increase in the respiratory frequency and in the respiratory amplitude. The effect of the stimulation increases with the duration of the stimulus, is comparable to the effect of carbon dioxide and shows ventilatory conditioned negative aftereffects. From the perifornical region a sort of paroxysmal tachypnea is obtained which is characterized by the sudden onset of a high respiratory frequency, with hardly increased or actually decreased respiratory amplitude and a displacement of the respiratory midposition toward the expiratory side. This tachypnea accompanies general affective reactions, such as piloerection, arching of the back, mewing and spitting, reactions which are obtained from this same region with stronger stimulation.

From the interthalamic commissure and from the lateral thalamus—lateral, ventral and caudal to the perifornical activating region—an electrical stimulus always causes a reduction in the respiratory frequency. With stimulation of the interthalamic commissure this is, for the most part, caused by a lengthening of the duration of inspiration. With stimulation of the lateral hypothalamus both phases, the inspiratory and the expiratory, are generally lengthened, and the respiratory amplitude is often reduced. In many cases the respiration has a dyspneic character, with increased simultaneous widening of the nostrils during inspiration, so that one must consider the possibility of a bronchoconstrictor effect with secondary changes in the respiration (95).

In connection with the diencephalon and mesencephalon one should also mention panting. Excitation of the hypothalamic thermal center leads, in the dog and in the cat, to an increase in the respiratory frequency up to 300 per min. which results—in spite of the reduction in respiratory volume—in an increase in the minute volume and an increased excretion of carbon dioxide. Panting can be elicited in the anesthetized dog by means of high-frequency thermal stimulation. Magoun and coworkers (129) state concerning this: "In the telencephalon the responsive region occupies a position between the anterior commissure and the base of the brain. Throughout the

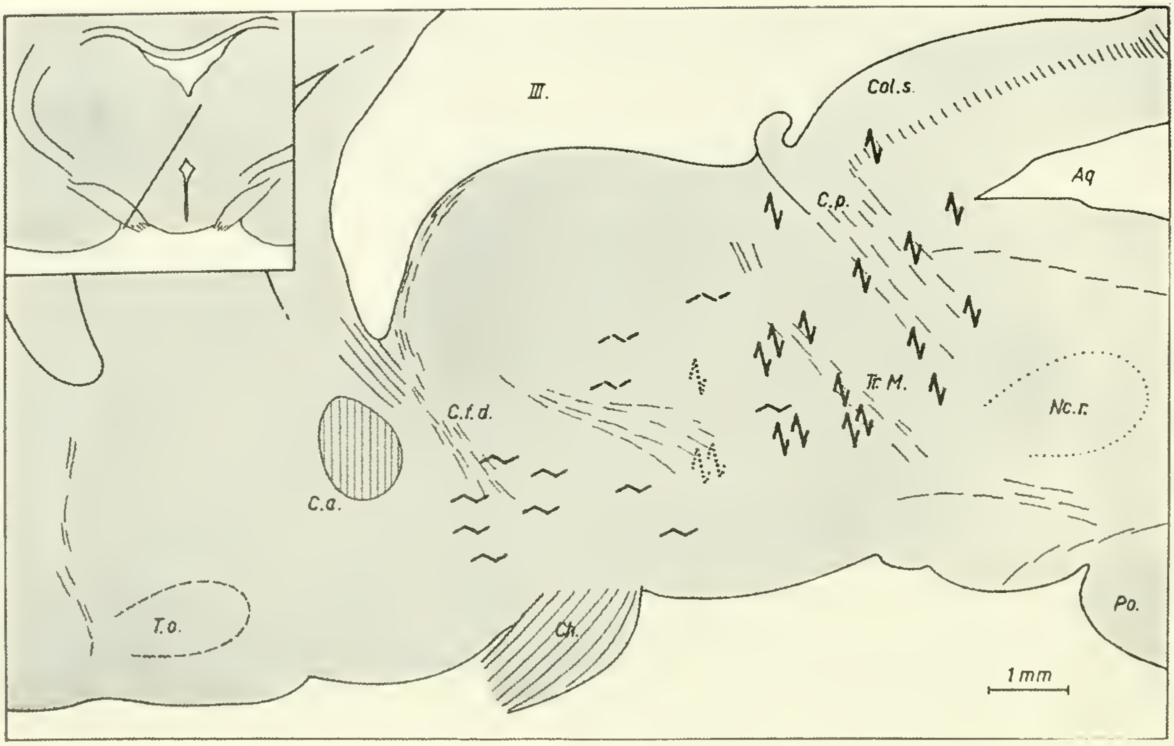

FIG. 2. Diagonal section through the anterior brain stem of the adult cat showing respiratory reactions to electrical stimulation. In the *upper left corner* the plane of the diagonal section is indicated on a frontal section. ϟ indicates an increase in respiratory activity, i.e. in the rate and amplitude of respiration. ∾ indicates a decrease in respiratory activity *Dotted symbols* represent points lying 1 mm medial to the plotted plane; *interrupted symbols* represent points lying 1 to 2 mm lateral to the plotted plane. *Aq.*, aqueductus sylvii; *C.a.*, commissura anterior; *C.f.d.*, columna fornicis descendens; *Ch.*, chiasma opticus; *Col.s.*, colliculus superior; *C.p.*, commissura posterior, *Nc.r.*, nucleus ruber; *Po.*, pons; *T.o.*, tuberculum olfactorium; *Tr.M.*, tractus Meynert; *III.*, ventriculus tertius. [Modified from Hess (91).]

diencephalon it is located in the dorsal part of the hypothalamus and the ventral part of the thalamus. At the anterior end of the midbrain it is located in the vicinity of the central gray matter, surrounding the transition from the third ventricle to the cerebral aqueduct." According to investigations on the unanesthetized cat with electrical stimulation and electrolytic tissue destruction (96), the region from which panting can be elicited seems to be rather extensive. It is more or less identical with those areas from which, in the mesencephalon, diencephalon and the supraoptic region, general respiratory activation is obtained.

Cortical and Cerebellar Influence on Respiratory Activity

The known fact that respiratory activity can be voluntarily controlled—in voluntary breath-holding, hyperventilation, speech and singing—stimulated, towards the end of the last century, a series of investigations of the cortical influences on respiration (69, 137, 179). From the already extensive literature dealing with the subject [for reviews see Dell (55), Kaada (107) and Smith (177)], one can, to begin with, conclude that the results of stimulation are to a large extent dependent on the depth and type of narcosis, on the type of current used as stimulus, and on the animal species. In spite of this, it would seem that the oral region of the frontal lobe is that part of the brain from which the respiration can be influenced without strong concomitant motor and vegetative effects (55, 93, 108). Less constantly obtained are respiratory changes initiated through stimulation of the ventral surfaces of the temporal lobe (157). On the other hand, circumscribed regions of the premotor area powerfully influence respiration, but their stimulation

also causes simultaneously general changes in muscle tone (107, 188). It is for this reason that the interpretation of respiratory effects with stimulation of the cortex is so difficult, particularly in the anesthetized and restrained animal. Thus, in the following discussion, only the most frequently observed respiratory effects will be mentioned.

Most easily obtained through cortical stimulation is a respiratory inhibition, with a decrease in the depth of inspiration and a prolongation of expiration. With stronger stimulation, a respiratory arrest can occur in expiration lasting for the entire duration of the stimulus. As shown in figure 3, the corresponding excitable regions are, in the cat, the gyrus orbitalis and gyrus proreus (13, 94, 177), the anterior part of the cingulate gyrus (inferior to the genu corporis callosi) (94, 178), and, with higher stimulus threshold, the sylvian and ectosylvian gyri (69, 177, 178). In the dog approximately the same zones are described as inhibitory to respiration and in *Macaca rhesus* or *mulatta* inhibitory zones are described, more or less in agreement with these, in the posterior orbital gyrus (13, 54, 107) and in the rostral and deeper portions of the cingulate gyrus (area 24) (107, 195). In man, for the most part, stimulation of the cortex results in an inhibition of respiration, for example from the orbital face of the frontal lobe (39), from the anterior end of the island of Reil (150) and from the columna fornicis (176).

Less densely located are regions from which a respiratory activation (inspiratory reaction) is obtained. The latter consists mostly, although not always, of an increase in respiratory frequency with an increase or decrease in amplitude. The occasionally observed respiratory arrests in inspiration are considered as maximal inspiratory activation and, therefore, are also included in this group. Respiratory activation is obtained in the dog and in the cat from the anterior sigmoid gyrus (107, 177) as well as from the anterior and middle portions of the cingulate gyrus (178). In the monkey the region with inspiratory reactions is located in an area rostral to the sulcus precentralis superior which cytoarchitectonically corresponds to area 6a (107, 177).

The course of the descending pathways for the cortical control of respiration has as yet been little investigated. For the most part, the connections from the cortical regions activating respiration to the septum and to the hypothalamus are at present being traced (55, 157, 176).

From the few reports dealing with the cerebellar influence on respiration one may conclude, from ablation experiments on the decerebrate dog (184) and from stimulation experiments on the cat (135, 136), that inhibition of the tonus of the inspiratory muscles and dampening of the chemoreceptor reflexes can be initiated from the anterior lobe.

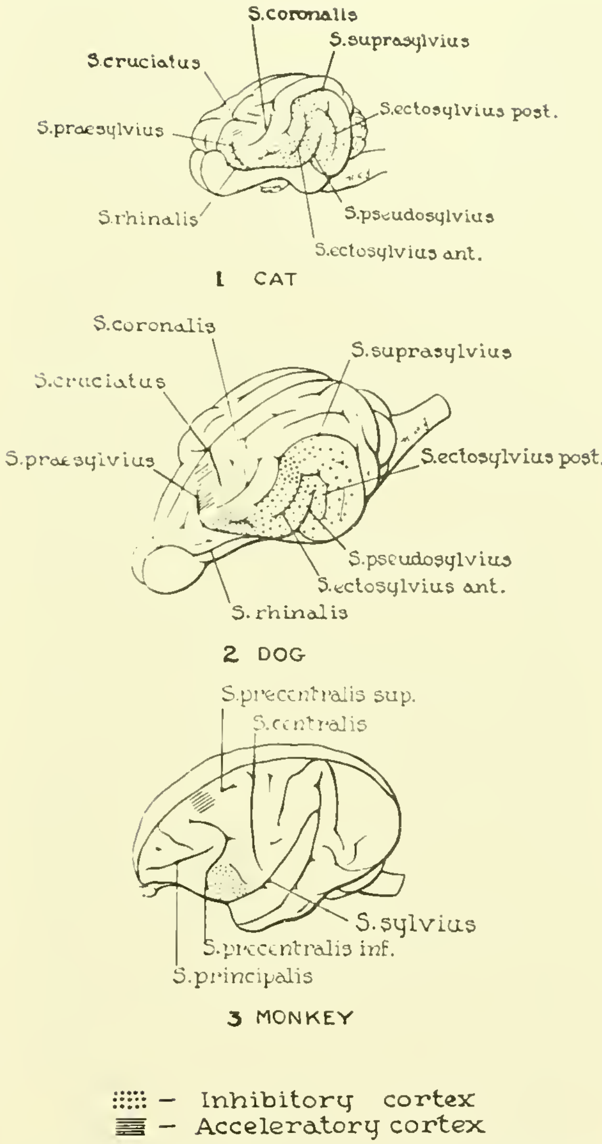

FIG. 3. Areas of the cerebral cortex from which alterations of respiratory movements were elicited by electrical stimulation. The *closest stippling* and the *closest lines* indicate the areas from which the responses were most easily obtained. [From Smith (177).]

Spinal Respiratory Centers and Descending Respiratory Tracts

Towards the end of the last century investigations were published in which animals were reported to be

able, after severance of the spinal cord at a high level, to maintain—spontaneously or after previous treatment with strychnine—a rhythmic, although ventilatorily inadequate, respiration (120, 197). The presence of spinal respiratory centers which are capable of originating rhythmic impulses (24, 86) and of reacting to stimulation by carbon dioxide (198) was therefore assumed, particularly in young animals. In older animals, however, the bulbar centers take over the respiratory regulation, so that respiration generally ceases after high severance of the spinal cord.

Some of the respiratory tracts which connect the pontine and bulbar centers with the motoneurons of the diaphragm and intercostal muscles, according to experiments in which the cervical cord was blocked (158, 187) or stimulated (162, 165), are located in the lateral column and end, for the most part, on the homolateral side. However, in view of the so-called 'crossed phrenic phenomenon,' a crossing to the contralateral side at the spinal level must be assumed (158). Porter (158) demonstrated in dogs the cessation of contractions in the left half of the diaphragm after ipsilateral hemisection of the cord at the level of the fourth cervical segment. When, following this, the right phrenic nerve was severed so that the right side of the diaphragm became paralyzed, strong contractions of the left side immediately appeared. This is evidently the manifestation of an influence from the bulbar respiratory centers which descends in the right side of the spinal cord and crosses over to the opposite side. Why this innervation comes into play only when the phrenic nerve on the side contralateral to the hemisection is severed is not quite clear. The phenomenon certainly depends in part on the absence of the phrenic afferent impulses. This subject has been reviewed by Dolivo (58).

Descending respiratory tracts are also found in the anterior column, for a complete respiratory paralysis occurs only when, after severance of the anterior part of the lateral columns, the anterior columns are also severed (151, 187). In the dog, Rothmann (167) believed that the paths to the phrenic motoneurons run in the anterior part of the lateral column (the ventrolateral column) and that the anterior columns contain the efferent paths to the intercostal muscles. A separation into inspiratory and expiratory efferent paths was attempted by Pitts (151) in the cat; lesions were placed either in the inspiratory or in the expiratory center in the medulla and the degeneration of the axons in the descending fiber bundles was followed with the Marchi method. In these experiments degenerated fibers were found in the above-mentioned columns, but a separate path for the inspiratory and the expiratory fibers could not be demonstrated. After destruction of the ventral quadrants of the cervical cord, cell degenerations were found in the inferior reticular nucleus of the medulla, i.e. in the region of the respiratory centers.

INTRINSIC CONTROL OF RESPIRATORY ACTIVITY

The question of the origin and mechanism of the rhythmic alternation between inspiration and expiration has intrigued investigators for many years and, according to the direction of the investigation undertaken, either humoral or nervous regulating mechanisms have been postulated. Since this section is concerned with the nervous regulation of respiration, it will be necessary to forego a discussion of the so-called chemical control of respiration. But, even with this limitation, the literature on the subjects is so extensive that, for a review of the older literature, the reader is referred to the summaries by Hess (89) and by Cordier & Heymans (46).

Assumed Mechanisms Leading to Rhythmic Respiration

Most investigators in attacking the problem proceed from the fact that in eupnea only the inspiratory phase is active, while expiration occurs passively. Eupneic respiration can be explained through two possible mechanisms; either the inspiratory center possesses the capability of sending out impulse salvos in periodic intervals, or a continuously active inspiratory center is rhythmically blocked by a neighboring or superimposed inhibitory center. The first possibility could be admitted if with quiet respiration the neuronal activity in the medulla oblongata occurred predominantly during the inspiratory phase. As a matter of fact, neurons which discharge during inspiration have been demonstrated (56, 189), but one finds just as many neurons which discharge continuously; on the other hand, only a few are active during expiration. A concentration of points showing activity synchronous with inspiration has been reported in the neighborhood of the nucleus hypoglossi and the caudal part of the nucleus ambiguus (1), and in the vicinity of the bulbar trigeminal nucleus (189). Of these regions, however, neither the nucleus hypoglossi nor the caudal nucleus ambiguus belongs to the respiratory center proper since they are the point of origin for efferent motor fibers. Thus it would seem that the investigations of electrical activity do not

speak unequivocally for the existence of a rhythmically active inspiratory center. Therefore, the conception of an inherent rhythmicity of a narrowly circumscribed and relatively simply constructed respiratory center has, in general, been abandoned.

The second possibility—periodic inhibition of a tonically active inspiratory center—represents a plausible working hypothesis. The intervention of an inhibitory or expiratory center also permits a better explanation of how, under certain circumstances, not only an inspiratory arrest but also an active expiration can take place. Pitts (155) and Wyss (208) have developed, in their detailed review articles, more or less similar conceptions of this intrinsic neuronal mechanism of respiration which are also in agreement with newer neurophysiological concepts.

The inspiratory center in the medulla is tonically active and emits impulses continuously. This would explain why, after a hypocapnic apnea, a tonic base activity develops in the phrenic nerve before any rhythmic activity is observed (206). The apneusis occurring after transverse section of the pons can be interpreted as a liberation of the automatically active inspiratory center from inhibitory influences. To support the theory of a primary inspiratory autonomy, stimulation experiments have also been carried out in the nucleus reticularis ventralis (inferior) of the medulla with the result that a strong inspiratory tetany, or a direct facilitation of the phrenic motoneurons, has been obtained (7, 18, 43, 151, 152, 154). From injection experiments with solutions of bicarbonate containing carbon dioxide (43), one may conclude that the nervous substrate with maximal sensitivity for carbon dioxide lies in the region of the inspiratory center. Slow potential waves can be obtained from this region under the influence of carbon dioxide (6.5 per cent in the inspired air), even in the fully denervated medulla. These potentials have been designated as 'slow medulla chemopotentials' (124, 190, 191).

This locally originating inspiratory tonus is then modulated through two (155, 163, 164) or three (208) inhibitory processes and transformed into a series of rhythmic events. To begin with, an intramedullary control mechanism must be assumed, since the apneusis which occurs after bilateral vagotomy and transverse section through the pons is transformed into rhythmic respiration by an additional transection through the striae acusticae, caudal to the trapezoid bodies (27, 101, 130). The inspiratory center, as postulated, sends out impulses, descending not only to the motoneurons of the inspiratory muscles but also to the bulbar expiratory center, and excites this through as yet undefined connections. Since this expiratory center requires a high degree of summation, it takes a certain amount of time before it is sufficiently activated. During this time the inspiration is completed. As soon, however, as the expiratory center begins to discharge, the inspiratory center (through an intramedullary process) and the inspiratory motoneurons (through a bulbospinal tract) become blocked. With a sufficiently high excitation of the expiratory center, the expiratory muscles are also excited. For the inspiratory motoneurons this can be looked upon as a form of reciprocal inhibition. With the decrease in the activity of the inspiratory center, the excitatory influence on the expiratory center disappears, the inhibitory influences of this center diminish, and the inspiratory center begins again to send out impulses in rapidly increasing succession.

An experimental proof for such an intrinsic self-regulating loop mechanism as has been described is, up to the present, lacking; and the two assumptions made in the concept of an interneuronic genesis of respiratory rhythmicity are defined by Wyss (208) as follows: "The one refers to the time lag inherent to the postulated interneuronic control, the other is concerned with what may be called the 'characteristic' of this control. The latter apparently does not follow a steady course but shows somewhere a critical level for the inhibition of, as well as for the release from, tonic inspiratory activity. Variations of the rate and depth of breathing would then be accounted for by changes in the reaction time of such as intrinsic control in either direction."

Corresponding to this intermedullary control mechanism is a second, pontobulbar inhibitory mechanism. The pneumotaxic center is believed to be excited either from the inspiratory center in the medulla (155) or from the apneustic center in the pons. Here also it can be assumed that the influence of the pneumotaxic center inhibits inspiratory activity, but that the influence lasts only so long as a maximal excitatory state prevails in the center. The inhibition of inspiratory activity can then result either from a blocking of the apneustic center, so that an activating influence on inspiration is suppressed, or from an intensification of the activity of the inhibitory (expiratory) center in the medulla.

This point of view is supported, above all, by the occurrence of apneusis after removal of the pneumotaxic center through a transection in the cranial third of the pons. Not fitting in with this scheme, however, is the assertion that electrical stimulation of the locus

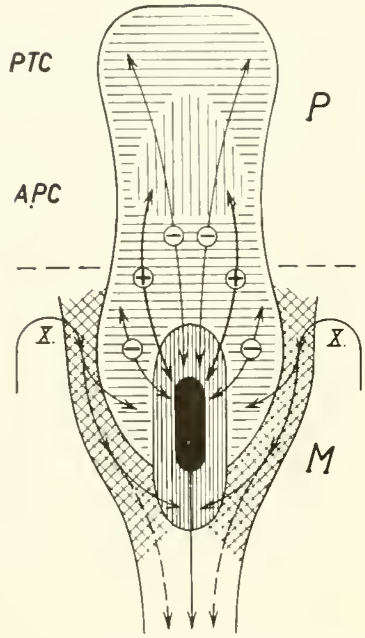

FIG. 4. Functional scheme of respiratory center. The primary inspiratory mechanism is shown in *black*. *Vertical hatching* indicates the inspiratory-facilitating component of intrinsic control (including in the pons the assumed apneustic center, *APC*). *Horizontal hatching* indicates the inspiratory-inhibiting (expiratory) component of intrinsic control (including in the pons the assumed pneumotaxic center, *PTC*). *Crosshatching* indicates the extrinsic control (solitary system). *X* designates the vagus nerve. The *horizontal broken line* separates the pontine level (*P*) from the bulbar level (*M*). [From Wyss (208).]

coeruleus, in which the pneumotaxic center has recently been localized, produces predominantly inspiratory reactions (16, 105), while expiratory effects are more easily obtained from deeper lying structures. The validity of the postulation of a pneumotaxic center would seem, therefore, to require further clarification.

A third mechanism, which can also lead to a transformation of tonic inspiratory activity into a rhythmic one, is seen in the vagal control reflexes (see the later section on extrinsic control). Therefore, in the schematic representation appearing in figure 4, the two closely associated central control mechanisms and the vagal-proprioceptive mechanism are presented as a functional unity. Since three different mechanisms guarantee respiratory rhythmicity, it is understandable that an isolated interruption of the pontine control need not always lead to a disturbance of the respiratory rhythm and that, after bilateral vagotomy, the respiration in most animals may continue rhythmically. However, in such cases, the medullary centers are much more easily deranged. For example, in deep narcosis and under morphine (28, 102, 175), in oxygen lack, and in states in which the arterial pressure is reduced (31, 32), respiratory patterns of the Cheyne-Stokes or Biot type can easily occur, in man as well as in experimental animals, and under certain circumstances a sudden respiratory failure is seen.

An interpretation varying from the above-developed conceptions has been advocated by Rijlant (163, 164). On the basis of his stimulation experiments in the medulla oblongata and in the spinal cord, with simultaneous registration of phrenic action currents, he believes that one must locate the origin of inspiratory tonus in a pontine center (the apneustic center of Lumsden). The continuous activity from this center, which of itself does not lead to a manifest inspiration (*respiration occulte*), would then be modulated, i.e. physically furthered or inhibited, from the medullary region (*centre bulbaire modulateur*).

Intrinsic Mechanisms Leading to Modification of Basic Respiratory Rhythms

The basic rhythm developed by the bulbopontine respiratory centers is modified through various influences. The most important of these, affecting the depth and rhythm of respiration, is the partial pressure of carbon dioxide in the blood. Its increase produces, either directly or through a reflex mechanism, a general activation of the medullary, pontine and spinal respiratory neurons. The mechanism of the direct action on the respiratory center is still open to discussion. In general, it is assumed that carbon dioxide in molecular form exerts a direct effect on the nerve cells in the center (43, 140, 172). Other authors postulate an indirect effect on the cell activity through a change in the pH of the intercellular fluid (14, 80, 202–204) or through a change in the intracellular hydrogen ion concentration (75, 76). However, since the pCO_2 and the extra- and intracellular pH are closely related to one another, the discussion has more academic than practical interest, especially since, up to the present, no central pH receptors have been discovered.

An increase in the activity of the inspiratory center under the influence of carbon dioxide leads, at first, to an increase in the depth of inspiration, and at the same time also to a stronger and more rapid excitation of the pneumotaxic and expiratory centers. This causes a more rapid change-over to expiration and, thereby, an increase in the respiratory frequency. When the degree of excitation in the expiratory center

is high enough, an active expiration results and the respiratory volume is increased, as seen, for example, in dyspnea.

A further influence on respiratory activity, always ascertainable in the intact animal, is of cortical origin. These psychic influences are of a manifold nature. Thus it has long been known that in the course of intellectual work the respiratory frequency increases, and the amplitude tends rather to be reduced (20, 53, 185, 194). Emotional changes are also often first detected by the observer through changes in the type or frequency of respiration (26, 211). These changes in the respiration can, at times, be so pronounced that they may be interpreted as an indication of certain psychic disorders (34, 63).

The influence of the diencephalic and mesencephalic centers on respiration has been discussed in detail in the first section of this chapter. Apparently we are here concerned with the intervention of a superimposed regulatory system, in connection with a general increase or decrease in the activity of the organism as a whole. For this purpose it seems expedient that when the metabolism, circulation and muscle tone are altered, respiration is also influenced in a corresponding manner (90, 92).

Respiratory Neural Discharge

The possibility of investigating nervous and muscular activity through the measurement of action potentials allows us to gain a more intimate insight into the innervation patterns of the respiratory muscles. Up to the present, the investigation of the innervation of the most important inspiratory muscle, the diaphragm, has been particularly thorough. For this purpose it is sufficient to record the electrical activity of the phrenic nerve, for—apart from a delay of about 10 msec.—practically synchronous potential waves are found in the phrenic nerve and in the diaphragm (72).

Action potentials from single fibers of a phrenic nerve root (3, 159), or from isolated fibers in the frayed nerve trunk (152, 153), exhibit most easily the pattern of the diaphragmatic innervation. During inspiration in eupnea, impulse series of relatively low frequency (10 to 30 per sec.) are found. The frequency of the action potentials usually increases slightly from the beginning to about the middle of inspiration and then remains approximately the same until the end of inspiration. With the beginning of expiration, the discharge salvo is, as a rule, suddenly discontinued. Under dyspneic conditions (3), or with stimulation of the inspiratory center in the medulla (152), the discharge frequency can increase to 100 or more per sec.; in fact, maximal frequencies as high as 400 per sec. have been recorded (159). With stimulation in the inspiratory center, moreover, the separate inspiratory phases are lengthened. On the other hand, stimulation in the expiratory region of the medulla shortens the duration of the salvos or blocks the neurons completely.

The action potentials present a more complicated picture when they are recorded from the central stump of the intact phrenic nerve. In eupnea a certain base activity is often seen during expiration (206) which would correspond to the tonic innervation of the diaphragm and on which the inspiratory activity is superimposed. Under the influence of carbon dioxide in addition to the increase in frequency in the individual nerve fibers already described, a recruiting of hitherto inactive neurons can be demonstrated, in the frayed as well as in the intact nerve (153, 155). Thus, the regulation of the depth of inspiration occurs through two mechanisms: an increase in the discharge frequency of the individual neurons, and an increase in the number of discharging neurons. Moreover, in extreme dyspnea (resulting from collapse of the lungs after bilateral vagotomy, or inhalation of 20 to 40 per cent carbon dioxide in oxygen), a marked synchronization can be observed. This is expressed in the electrical pattern through the occurrence of waves which are absolutely synchronous in both phrenic nerves and—whenever present—also in the vagal efferents (209).

A rhythmic activity can be demonstrated not only in the phrenic nerve and diaphragm, but also in the other respiratory muscles and the nerves supplying them. Thus Bronk & Ferguson (29) were able to demonstrate in decerebrate cats, that those intercostal nerve fibers which run to the external intercostal muscles (with the exception of the interchondral portion) discharge only during inspiration. On the other hand, fibers which innervate the internal intercostal muscles discharge only during expiration.

Electromyographic studies in man (35–37, 106, 145) have demonstrated that during quiet respiration, in addition to the diaphragm, only the scalene muscles show an increase in activity during inspiration, while expiration occurs passively. But during voluntarily forced or dyspneic respiration, the muscles listed in the following table may be innervated.

Expiratory muscles	*Inspiratory muscles*
M. rectus abdominis	M. diaphragma
M. obliquus abdominis ext.	Mm. scaleni
M. obliquus abdominis int.	M. serratus post.
M. pectoralis minor	M. intercostalis externus pars interossea, I to V.
M. intercostalis externus, pars interossea, VI to X.	M. intercostalis externus, pars intercartilaginea
M. intercostalis internus, pars interossea et pars intercartilaginea, VI to VIII.	M. intercostalis internus, pars intercartilaginea, I to V.

EXTRINSIC CONTROL OF RESPIRATION

A variety of nervous influences can further or inhibit the automatic activity of the bulbopontine respiratory centers. Thus the stretch receptors in the lungs and the chemoreceptors of the glomus caroticum are directly connected with the respiratory centers through afferent fibers in the vagus and glossopharyngeal nerves. For other receptor regions the connection to the medulla is less distinct.

Vagal Control of Respiration

VAGAL PROPRIOCEPTIVE CONTROL. After bilateral severance, or reversible blocking, of the vagus nerves in the neck, the respiratory frequency decreases while the amplitude increases. The minute volume is, therefore, usually hardly changed. But the immediate result of vagal blocking is so strongly dependent upon the technic used, the type of narcosis and the animal species that quite contradictory statements on the effects of vagotomy can be found in the literature. In rabbits, cats and dogs, an inspiratory reaction (lengthening of the duration of inspiration and an increase in lung volume) has been described by those authors who attempted to block the vagus through cooling (70, 81, 123, 125). On the other hand, after vagotomy or electrical blocking, expiratory reactions or even long periods of respiratory arrest in expiration have been described (110, 111, 114, 166); but, regardless of the effect of the interference between the loss of innervation on the one hand and a momentary stimulation on the other, tracheotomized animals breath more slowly after bilateral vagotomy than before. Therefore, an effect tending primarily to increase the respiratory frequency has been ascribed to the vagus. As is shown in figure 5, this frequency-enhancing influence is especially pronounced in the guinea pig (144).

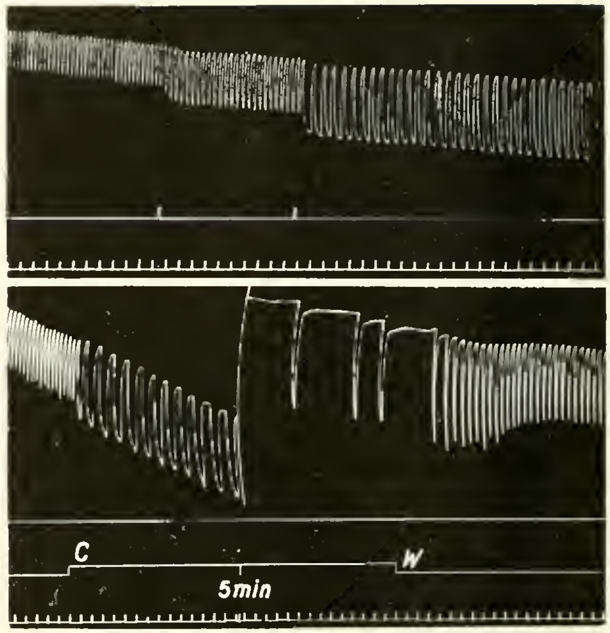

FIG. 5. The effect of vagotomy and of cooling of the vagus nerve on respiratory rate and amplitude. *Upper record:* One vagus cut at first signal, other at second. Rabbit under urethane narcosis. Respiratory frequencies: 60, 50 and 30 per min.; tidal air: 24, 32 and 45 ml, pulmonary ventilation: 1440, 1600 and 1350 ml per min. before vagotomy and after unilateral and bilateral vagotomy, respectively. *Lower record:* Guinea pig under Numal narcosis. The left vagus was sectioned and the right vagus cooled to 4°C. Registration was interrupted for 5 min. in the middle of the kymogram. At the end of the signal (*W*) the vagus was rewarmed. Prolonged vagus interruption causes extreme reduction of respiratory frequency in this animal. In both figures inspiration is downwards. Time marks are 3 sec. apart. (Original records prepared by R. J. H. Oberholzer.)

The current concepts of the role of the afferent vagal fibers from the lung are based, however, not so much on vagotomy experiments as on the classic investigations by Hering & Breuer (85), Gad (70) and Head (83, 84). These authors demonstrated that, after closure of the trachea at the end of an inspiration, the following expiration lasts considerably longer than the preceding one. Conversely, when the trachea is closed at the end of an expiration, the following inspiration is prolonged. Furthermore, inflation of the lungs leads to a reflex expiration, while the aspiration of air from the trachea or the application of a pneumothorax elicits an inspiratory reflex. In the apneic animal with an open thorax, an elevation of the diaphragm has been observed upon inflation of the lungs, a lowering of the same with collapse of the lungs (88). All of these reflexes are interrupted, or at least considerably diminished, by vagotomy. Hering & Breuer assumed, therefore, that two reflex effects are mediated

through the vagal nerves: with the expansion of the lungs an inhibition of inspiratory and furthering of expiratory activity; with the diminution of the lung volume an exactly opposite influence.

Some insight into the mechanism of such a respiratory regulation has been afforded by action potential investigations (2, 49, 112, 146–149). Distention of the lungs produces an increase in electrical activity in the intact trunk of the vagus, as well as in the frayed nerve, which has been attributed to the stimulation of stretch receptors in the lung. The exact location of the receptors is not yet known; it has been suggested as subpleural (196) or as peribronchial (199, 200). The frequency of the action potentials in the isolated nerve fiber, and the number of stimulated nerve elements, is directly proportional to the rapidity with which the increase in lung volume results (49) and to the degree to which the lungs are distended. This would seem to be valid, in principle, for both types of receptors investigated up to the present, the slowly adapting (2) and the rapidly adapting stretch endings (112). During inspiration the receptors discharge with an impulse frequency up to 100 per sec.; during expiration many elements cease discharging altogether, others discharge with at most 30 impulses per sec. It has been assumed that with the increase in the number of afferent impulses in the vagus the inspiratory center is increasingly inhibited, so that a shortening of the duration and a decrease in the depth of inspiration results (2, 153, 155). When this inhibition is abolished through bilateral vagotomy, the inspirations become longer and deeper.

But the inhibition of inspiratory activity cannot represent the only function of the vagal fibers from the lungs, for stimulation of the central stump of the vagus (with stimuli only slightly above threshold and a stimulus frequency between 20 and 40 per sec.) elicits either a more or less pronounced tonic inspiratory reaction or an acceleration of the respiration, depending on the animal species. On the other hand, with stimulus frequencies between 100 and 300 per sec., a lengthening of the expiratory phase and a decrease in the depth of inspiration is obtained. This dependence of the result of afferent vagal stimulus on the frequency has up to now been demonstrated in the rabbit (205), the cat (161, 180), the monkey (207) and the guinea pig (143, 144). It has been particularly well investigated in the rabbit. In this animal, action potential measurements on the cranial stump of the electrically stimulated vagus, with simultaneous registration of a pneumogram, have demonstrated that the reflex reversal appearing with increase in the stimulus frequency can be elicited by stimuli just strong enough to excite the α and β fibers but which is subliminal for the more slowly conducting fibers. With stronger stimuli (three to four times the threshold intensity for α fibers), a stimulation with low frequencies produces a more marked inspiratory effect, occasionally an inspiratory tetanus. A higher frequency of stimulation can then result in a respiratory arrest in expiration with active participation of the expiratory muscles. In both cases, however, the more slowly conducting δ fibers are always excited.

On the basis of these experiments, Wyss (208) believes the Hering-Breuer reflex is due to a central stimulation from stretch receptors which can discharge with a high or a low impulse frequency, depending on the degree of distention of the lungs. The assumption is then made that the inspiratory center requires a lower degree of summation than the expiratory center, so that it can be activated by afferent stimulation of a lower frequency. An inhibition of inspiration occurs only when, as a result of increasing temporal and spatial summation, the expiratory center becomes sufficiently activated to exert an inhibitory influence on the inspiratory center (fig. 6). For

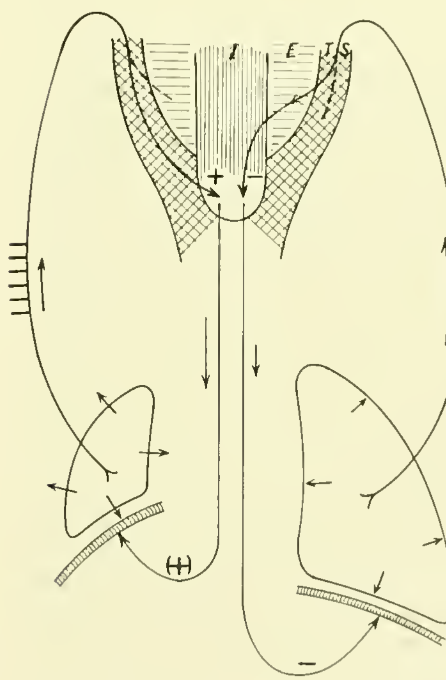

FIG. 6. Schematic representation of weak inspiratory-facilitating reflex from small lung volume (*left*) and strong inspiratory-inhibiting (expiratory) reflex from large lung volume (*right*). *I*, bulbar inspiratory center; *E*, bulbar expiratory center; *IS*, solitary tract system. [From Wyss (208)]

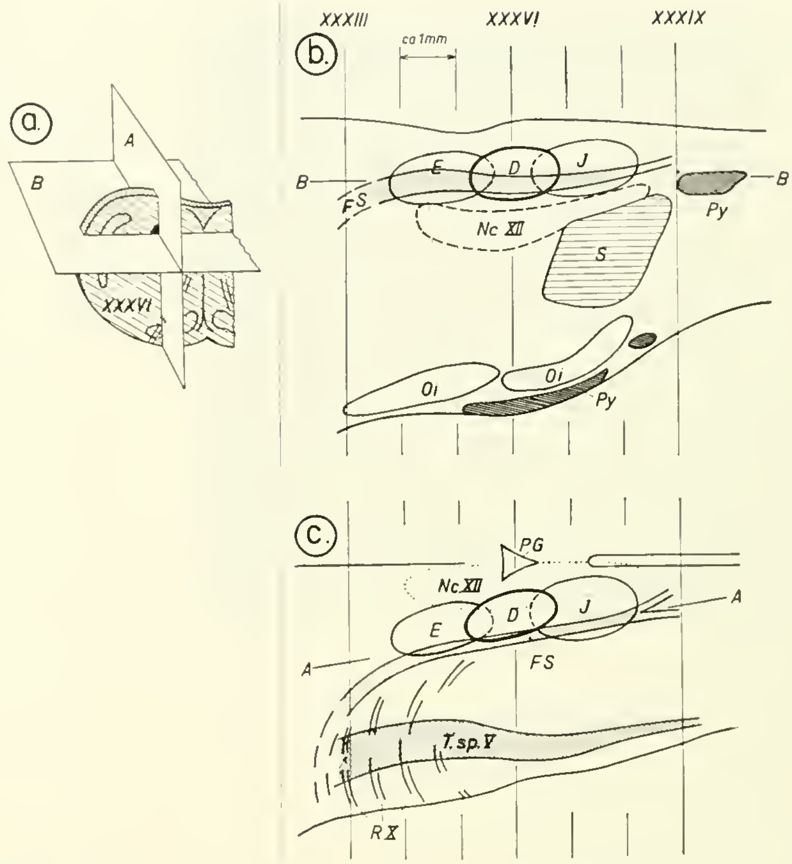

FIG. 7 *a*: Horizontal section through the medulla showing the location of the vertical and horizontal planes drawn in *b* and *c*, respectively. *b* and *c*: Location of the vagal reflex centers in the medulla of the rabbit relative to the fasciculus solitarius (*FS*), the nucleus of the hypoglossal nerve (*Nc.XII*), the inferior olive (*Oi*), the decussation of the medial lemniscus (*S*), the descending pyramidal tract (*Py*) and the spinal tract of the trigeminal nerve (*T.sp.V*). Relay stations for vagal expiratory (*E*), aortic depressor (*D*) and vagal inspiratory (*J*) reflexes on the medial border of the solitary bundle at the level of the promontorium gliosum (the abex, *PG*). [From Oberholzer (141).]

the proprioceptive control of respiration only the rapidly conducting components of the vagus nerve are considered important. They are believed to establish contact with the inspiratory as well as the expiratory center through an as yet unknown manner of distribution and to stimulate both centers simultaneously. Slowly conducting fibers may be significant for the occurrence of a strong inspiratory reaction following collapse of the lungs or a stronger stimulation of the vagus (208), but their role in the vagal control of respiration is not yet clear. Evidence for the simultaneous action of the vagus fibers on both respiratory centers is seen in the appearance of rebound phenomena after expiratory reactions produced by stimulation of the vagus with higher frequencies.

In the rabbit it has also been possible to localize the relay centers for the vagal respiratory reflexes in the medulla. Through high-frequency electrocoagulation in the region of the caudal end of the tractus solitarius, a small zone can be eliminated following which electrical stimulation of the ipsilateral central stump of the vagus yields only the expiratory vagal reflex, but not the inspiratory reflex (142). Conversely, an expiratory region has been described lying 2 to 3 mm cranial from the obex and also belonging to the system of the tractus solitarius, the destruction of which causes solely the loss of the vagal expiratory reflexes (8). But these regions should not be designated as respiratory centers since their bilateral destruction causes only slight changes in the respiration of animals previously subjected to bilateral vagotomy. They have, therefore, been designated as relay stations for vagal respiratory reflexes. Their approximate location in relation to the nucleus of the hypoglossus nerve, the obex and the inferior olive, as well as to the relay station for the aortic depressor reflexes, is diagramed in figure 7 (141). The actual respiratory centers lie, according to what has been said earlier, in the reticular substance of the medulla. They are connected with the reflex zones of the solitary tract through secondary neurons. The caudally and medially located inspiratory center would seem to be closely related to the inspiratory reflex center; the less sharply circumscribed, more cranially and laterally located expiratory center to the expiratory reflex center.

The discussion carried on for many years over the significance for respiration of the vagal fibers from the lungs seems thus to have more or less come to a close. In principle, the vagus can exert an inhibitory as well as a facilitating influence on inspiration. Depending on the animal species or the type of narcosis used, the one or the other effect predominates. In the cat, dog and monkey the inhibitory effect is dominant. In the rabbit the facilitating effect on inspiration is clearly in evidence, and in the guinea pig it is actually indispensable for the maintenance of the respiratory rhythm (144).

VAGAL CHEMORECEPTIVE CONTROL. The importance of the aortic, pulmonary and cardiac chemoreceptors for respiratory and circulatory regulation has recently been discussed by Dawes & Comroe in such a comprehensive review article (51) that only the more generally accepted concepts will be mentioned here.

After bilateral denervation of the carotid bodies, the excitation of the aortic chemoreceptors by carbon dioxide, anoxia, lobeline or piperidine leads to a reflex hyperpnea which is abolished by bilateral vagotomy (74, 99, 100). Experiments in which the various intrathoracic fibers of the vagus are interrupted have demonstrated that the afferent fibers from the aortic body run predominantly in the right depressor nerve in the cat (138), while in the rabbit they are found principally in the trunk of the vagus (103).

Small amounts of 0.5 *N* acetic acid, injected directly into the aorta, block the aortic chemoreceptors but not the pressoreceptors. Through this means, as well as through denervation of the aortic chemoreceptors, it has been demonstrated that these receptors are much less important than the glomus caroticum for the control of respiration.

One must differentiate the chemoreceptors proper (aortic chemoreceptors and glomus caroticum) from receptors in the lung which are also subject to chemical influence. Their exact location has not yet been determined, but a close association with the pulmonary blood vessels seems probable. These pulmonary 'chemoreceptors' can be stimulated by a great variety of substances; they produce a reflex apnea (in the cat and dog in expiration, in the rabbit occasionally in inspiration) followed by hyperpnea (50). For further research in this direction it would be advantageous, according to Dawes & Comroe (51), to define more sharply the concept 'chemoreceptor,' and to classify those substances which are able to influence respiration over pulmonary receptors into three groups, according to their mechanism of action: *a)* substances which excite the Hering-Breuer inflation reflex: veratrine, veratridine and other veratrum alkaloids; *b)* substances which excite the pulmonary respiratory chemoreflex: phenyl diguanidine, diphenhydramine, mepyramine, 5-hydroxytryptamine; *c)* unclassified substances, e.g. various other amidines and antihistamines, serum, nicotine, phosgene.

Role of the Carotid Body in Respiratory Control

Since the first descriptions of the carotid sinus as a chemoreceptive reflex zone (46, 98, 170, 171), the investigations by Comroe & Schmidt (44) and by Heymans & Bouckaert above all (97) have contributed to the fact that we now differentiate between pressoreceptors in the wall of the sinus caroticum and chemoreceptors in the glomus caroticum (carotid body). Both receptor regions are connected with the medullary centers through the Hering nerve, a branch of the glossopharyngeal nerve. A differentiation of the influences of the pressoreceptors from those of the chemoreceptors is relatively simple in the dog. The glomus caroticum can be cut off from its blood supply by ligation of the occipital artery at its exit from the external carotid artery, and the sinus region is easily denervated. In the cat and in the rabbit a separation of the two receptor regions is more difficult to accomplish. Moreover, the anatomical position (52) and the blood supply (42) of the carotid body vary from species to species.

Of the two types of receptors, the chemoreceptors are of primary importance for the reflex control of respiration. Stimulation of the afferent fibers from the carotid body leads—after a certain latent period—to a marked increase in the respiratory amplitude and, to a lesser extent, in the respiratory frequency. The following have been demonstrated, in numerous experiments, to act as physiological stimuli: decrease in the oxygen saturation of the arterial blood to below 85 per cent, increase in the arterial pCO_2 and lowering of the pH in arterial blood. Views are divergent only over the relative importance of the central and the reflex stimulation of the respiratory centers by carbon dioxide. The Heymans school (25, 97) considers the reflex activation of the respiration by carbon dioxide to be dominant and assigns a subordinate role to the direct effect of carbon dioxide on the respiratory center; but other authors (59, 173, 174) have demonstrated in the dog that the increase in respiratory minute volume produced by carbon dioxide is almost

as great after elimination of the chemoreceptors as before.

Action potential investigations on the intact and frayed Hering nerve in the cat have also disclosed the particular sensitivity of the glomic chemoreceptors to a deficiency of oxygen or an excess of carbon dioxide. A reduction in the oxygen saturation of arterial blood below 95 per cent Hb (10, 193), or an increase in the arterial pCO_2 above 30 mm Hg (15, 193), leads to an enhancement of electrical activity. Moreover, the discharge frequency has been shown to run almost parallel to the arterial pCO_2. A large loss of blood (119), a reduction of the systemic blood pressure below 40 to 50 mm Hg, or the stimulation of the cranial part of the cervical sympathetic trunk (47, 68) gives rise to a continuous discharge of the chemoreceptors as a result of the consequent local ischemia in the carotid body. The glomus caroticum can also be stimulated by lobeline, nicotine, acetylcholine and cyanide. The respiratory activation produced by these substances is often utilized as a means of determining whether or not the chemoreceptor reflex is functioning.

When both the glomus caroticum and the aortic chemoreceptors are eliminated, the respiratory minute volume is reduced by about 30 per cent. Thus one can, in general, assign to the aortic, and particularly the sinus chemoreceptors, a tonic facilitating influence on the respiratory center (74). Through their intervention or their suppression can be explained, for example, the hyperpnea following clamping of the carotid arteries (168, 171, 192), the reduction in the respiratory minute volume occasionally observed during inhalation of pure oxygen and the stimulation of respiration observed in oxygen deficiency states (21).

Pressoreceptor Influence on Respiration

The influence of the pressoreceptors on respiration is less marked than that of the chemoreceptors. In the dog, electrical stimulation of the aortic depressor nerve (113) or the physiological stimulation of the stretch receptors in the carotid sinus through increase in the intravascular pressure leads to a decrease in the respiratory frequency and amplitude or to respiratory arrest in expiration (98, 170). In general, therefore, an inhibitory influence of the pressoreceptors on respiration has been assumed (11). However, this assumption is not necessarily valid. For example, Swedish authors point out that even when experiments are carried out on the isolated perfused carotid sinus, the supply of oxygenated blood to the glomus caroticum may be impaired by the operative procedure. Furthermore, an increase in pressure within the carotid sinus not only causes a stimulation of the sinus nerve but can also lead to a higher flow rate through the carotid body. The decrease in chemoreceptive respiratory activation, resulting from better oxygenation of this organ, could simulate a pressoreceptive respiratory inhibition.

An effect of the pressoreceptors on respiration can, therefore, only be demonstrated when secondary compensatory reflexes have been eliminated. This has been attempted through the introduction of a blind sack in the sinus, through the automatic compensation of variations on the systemic blood pressure, or by allowing the experimental animal to breathe pure oxygen (23). With these procedures on cats and on dogs stimulation of the carotid sinus receptors produces only slight changes in respiration (22, 74); but even in these experiments one must consider the possibility of secondary compensatory reflexes since a strong expiratory inhibition is observed with the same stimulation following vagotomy (22, 23). This difference in the respiratory effects of carotid sinus stimulation in the vagotomized animals could be due to a concomitant bronchoconstrictor effect mediated through the vagus nerve (48, 201). An increase of resistance in the air passages leads, through vagal and other proprioceptive reflexes, to compensatory changes in the respiration. Therefore, it is possible that a secondary activation of respiration due to bronchoconstriction is able to mask the inhibitory effect of carotid sinus stimulation as long as the vagus nerves remain intact. The inhibition can only manifest itself when, as a result of vagotomy, the bronchoconstriction fails to take place.[1]

Proprioceptive and Protective Respiratory Reflexes

Under proprioceptive respiratory reflexes (in the narrower sense) are included those reflexes which have their origin in the respiratory muscles, the afferent pathways for which do not run in the vagus nerve. Tachographic investigations on man (64) and on dogs and sheep (65) have disclosed a number of compensatory respiratory reflexes against sudden changes of resistance in the air passages. An increase in resistance

[1] The findings by Winder (201) should not be interpreted as an inhibition of central respiratory activity, since the plethysmographic methods used allow merely a measurement of the flow resistance to the artificial respiration.

during the inspiratory phase leads to a lengthening of the inspiration and a development of greater strength in the inspiratory muscles. The converse is seen with an increase in resistance during expiration. With sudden removal of an obstruction in the air passages, the inspiration (or expiration) is reflexly shortened and there is a reduced development of strength in the respective respiratory muscles. The reflex is elicited through stimulation of stretch receptors in the diaphragm (38, 57) and in the intercostal muscles. It is also seen after bilateral vagotomy but is abolished by combined severance of the vagus and phrenic nerves and the posterior roots. The significance of these proprioceptive reflexes is seen in a reflex adjustment of the strength of the respiratory muscles to the flow resistance in the air passages. Moreover, they are believed to reinforce the Hering-Breuer reflex.

A number of protective reflexes are able to block respiration temporarily. The best known of these have their origin in the mucous membrane of the nose. They have been designated trigeminal protective reflexes (116). Irritating substances, e.g. chloroform or ether vapors, ammonia, tobacco smoke, acrolein, phosgene or hydrogen sulfide (116, 128), provided they do not penetrate beyond the upper respiratory passages, cause a slowing of respiration in low concentrations, a respiratory arrest in higher concentrations. These effects can lead to a complete cessation of respiratory activity so that electrical activity can be demonstrated neither in the phrenic nerve nor in the fifth intercostal nerve which is normally active in expiration (133). These protective reflexes are generally no longer present after severance of the trigeminal nerve. The occasional observance of considerably weakened protective reflexes can be explained by the fact that expiratory reactions are also obtainable by stimulation of the olfactory mucosa (4, 5). However, the inhibitory respiratory reflexes of olfactory origin are not as easily elicited as the activating olfactory reflexes since particularly aromatic and balsamic substances evoke a cortical activation of respiration (sniffing) in animals (6, 19). The sneezing reflex can also be elicited from the nasal mucous membrane (169). It can be obtained in the rabbit and in the cat by stimulation of the anterior nares, in man by touching the anterior or posterior end of the middle and inferior nasal conchae and corresponding parts of the nasal septum. The afferent pathways run in the ethmoidal branches of the nasociliary nerve.

A protective respiratory reflex occurring innumerable times every day takes place during swallowing. It consists essentially in a closure of the nasopharynx by the soft palate, a closing of the glottis and a raising of the larynx. The resulting respiratory arrest can occur in any phase of respiration. In animal experiments, electrical stimulation of the superior laryngeal nerve (181), or of the glossopharyngeal nerve (130), has led to swallowing movements and inhibition of respiration. Light contact with the palatinal and pharyngeal mucosa in the pentobarbitalized cat leads to an acceleration of respiration; stronger stimulation of the mucous membrane results in respiratory arrest in expiration (186). More recently, a reflex influence on respiration during the course of swallowing was demonstrated in the cat in urethane anesthesia by recording action potentials from neurons in the medulla which discharge synchronously with inspiration (or with expiration) (104). However, the sequence of the afferent and efferent impulses in the trigeminal, glossopharyngeal and vagus nerves has been so little investigated that only conjectures can be made about the central mechanism of respiratory control during swallowing.

One is probably dealing with a nociceptive reflex when, in the rabbit (78), dog (17) and man (118), a slowing of respiration or a respiratory arrest in expiration is obtained by stimulation of the afferent fibers of the splanchnic nerve. Occasionally an exteroceptive influence on respiration has been demonstrated, for example a deep inspiration, or respiratory arrest, with stimulation of the skin by cold, and respiratory activation (less often inhibition) with painful stimuli.

Hyperpnea Associated with Muscular Activity

According to what has been said previously, the nervous control of respiration has its origin in pontomedullary centers located in the reticular substance. Most of the neurons in the inspiratory center are automatically active and exert a tonic influence on the motoneurons of the inspiratory muscles. The degree of automatic activity is dependent upon metabolic processes; it is probably determined, above all, by the partial pressure of carbon dioxide or the hydrogen ion concentration in arterial blood or both. The continuous activity of the primary inspiratory center is transformed into a rhythmic one through medullary and pontine inhibitory processes, thereby leading to the alternation between inspiration and expiration. The respiratory rhythm is also controlled from the lungs over vagopulmonary (Hering-Breuer) reflexes. The activity of the medullary and pontine respiratory centers does not, however, follow a rigid

pattern; it is constantly being inhibited or facilitated through central nervous, reflex or humoral influences. Actually, the number of factors which can influence respiration in the intact animal is so great that virtually the entire organism can be said to contribute something to the control of respiration.

The complexity of the problem is best illustrated when one attempts to uncover the origin of the hyperpnea associated with muscular effort. This type of hyperpnea has commanded the interest of investigators for many years since very large respiratory minute volumes can be measured. Yet this increase in respiration cannot arise merely from a change in composition of the blood gases—in the steady state, for example, the arterial pCO_2 is lowered rather than increased. From the very beginning of research on this problem, four theories for the occurrence of increased ventilation with muscular activity were suggested. These have often been advocated even by more recent investigators.

a) The assumption was made that working muscles produce unknown metabolic products which stimulate the respiratory center, either directly or through a reflex mechanism (9, 73, 79). Such substances have occasionally been designated as 'hyperneine,' but their existence seems questionable (109).

b) It was suggested that 'work hyperpnea' could be elicited, through a reflex mechanism, by afferent impulses from active muscles and joints (61, 62, 82). In the dog, for example, leg movements evoked by stimulation of the ventral roots lead immediately to hyperpnea. This fails to occur when the spinal cord has been cut at the level of the tenth thoracic vertebra, or appears later in a weaker form—similar to the reaction in the cat before spinal cord section. In a similar manner, the hyperpnea produced in man through passive movements of the legs may be abolished by spinal anesthesia (45). The increased ventilation elicited by electrical stimulation of afferent fibers from joints and muscles (45, 60, 71, 210) also argues for the possibility of a reflex activation of respiration.

c) From the sudden onset of hyperpnea at the beginning of increased voluntary activity, a direct cortical influence on the respiratory center has been inferred (117, 134).

d) On the basis of excitability studies with carbon dioxide, the assumption has been made that muscular activity gives rise to a general enhancement in the sensitivity of the respiratory center to chemical and other stimuli (115, 117, 140). The more easily excitable respiratory center could then be activated in the presence of a lower pCO_2 in arterial blood. But the nature of this increase in sensitivity is as little understood as that of the greater sensitivity of the respiratory center towards carbon dioxide which occurs with acclimatization to high altitudes.

Considered alone, none of these suggested mechanisms entirely explains the occurrence of hyperpnea in connection with muscular activity. Therefore, one must assume that, in this case at least, chemical and nervous influences are both involved. From a teleological point of view, such a complex method of regulating respiration must be considered the more suitable, for only in this way can a ventilation be maintained which is capable of meeting widely varying bodily needs.

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CHAPTER XLIV

Central cardiovascular control

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CHAPTER CONTENTS

THIS SURVEY of our knowledge of the central nervous control of the cardiovascular system must necessarily omit discussion of important early works. The author has felt obliged to present his own interpretation of available data since space does not permit lengthy discussion of different points of view. Although electrophysiological data concerning the vasomotor apparatus are meager, they will be specially emphasized.

In spite of notable advances in techniques for study of the circulatory system and its nervous control since Tigerstedt's (203) manual appeared in 1923, further methodological development is a major need. Nervous control must eventually be described in terms of impulse traffic in afferent and efferent nerve fibers and synaptic routing. Electrophysiological techniques are still of limited value because of the small size of

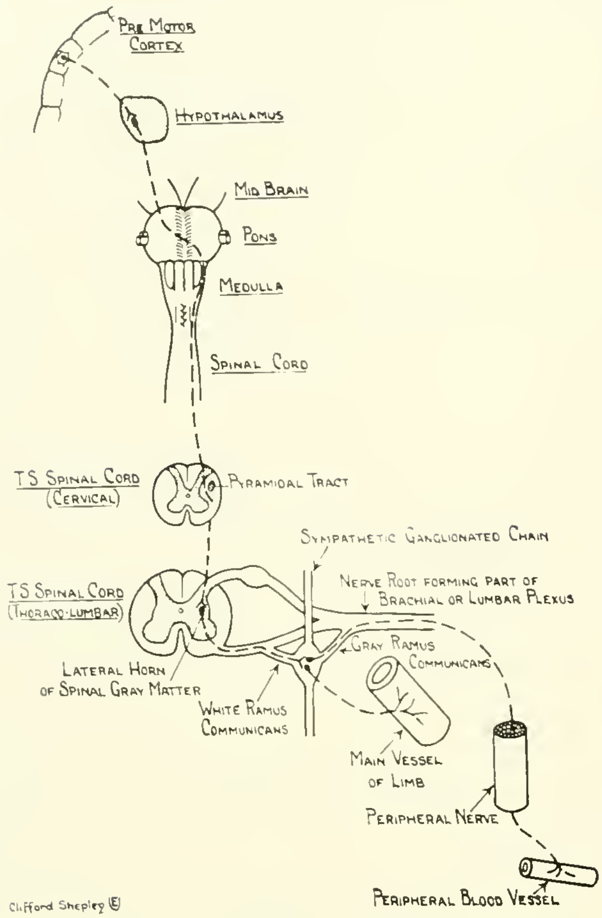

FIG. 1. Diagram of sympathetic vasomotor pathways to limbs. [From Richards (183).]

most of these fibers which makes their isolation and identification very difficult. This deficiency in electrophysiological knowledge is particularly to be regretted since recording of cardiovascular responses alone provides a very imperfect picture of the behavior of the neurons evoking them. Such responses, because of their sluggishness, do not reflect the effect of individual impulses in vasomotor nerves. In a vasoconstrictor fiber an impulse frequency as low as 1 to 2 per sec. is sufficient to produce a tonic contraction of the vessel wall.

It should be emphasized that variations in arterial pressure provide only a very limited picture of the peripheral vasomotor pattern. As Rein (182) often pointed out, major variations in the distribution of blood flow occur without any change in the arterial pressure level. Thus, stimulation of the hypothalamus activates the sympathetic vasodilator outflow causing a manifold increase in muscle blood flow. Since cutaneous and splanchnic constriction is also evoked, the total peripheral resistance and the arterial pressure are not altered (75).

Another limitation in much experimental work has been the use of anesthetized animals in which results probably are distorted by the absence or distortion of nervous compensatory mechanisms presumably active in conscious animals. Supplementary experiments in the absence of anesthesia are badly needed.

Thus, broadly speaking, the experimental basis o our knowledge of central cardiovascular control is weak in that it derives to a considerable extent from indirect and often inaccurate methods which have seldom lent themselves to quantitative evaluation of the nervous processes mediating this control.

EFFERENT PATHWAYS

Sympathetic Vasoconstrictor Nerves

PERIPHERAL DISTRIBUTION. The thoracolumbar sympathetic outflow distributes vasoconstrictor fibers to blood vessels throughout the body, both on the arterial and on the venous side. Only the capillary bed, the area between the precapillary sphincters and the venules, is considered to be devoid of an efferent innervation (and also contractile elements).

The pre-postganglionic relay stations for the bulk of the preganglionic outflow to the skeletal muscles and skin are in the paravertebral ganglia. The postganglionic fibers pass in the grey rami communicantes to the spinal nerves and ramify with the latter to their peripheral destinations. The diagram in figure 1 shows schematically the course of the vasoconstrictor outflow to the extremities. The intracerebral relay stations are not completely indicated. The proximal portions of the blood vessels of the extremities, the visceral vessels in the abdomen and the cerebral vessels receive the main part of their vasoconstrictor innervation directly from the postganglionic fibers running along the vessels. For particulars of the segmental distribution of the vasomotor innervation, reference should be made to manuals such as that of McDowall (162, 163).

Considerable interest attaches to the repeated reports, in recent years, of 'intermediary' sympathetic ganglia. Sympathetic ganglion cells have been histologically demonstrated in close connection with the ventral roots. Postganglionic fibers from such aberrant ganglion cells do not necessarily pass via the sympa-

thetic paravertebral ganglia and hence are not reached on extirpation of the latter [Wrete (226–228), Pick & Sheehan (174), Alexander *et al.* (11), Boyd & Monro (38), Randall *et al.* (178)]. A greatly reduced, though functional, central vasoconstrictor control might therefore persist even after 'total' sympathectomy. If so, then we would have an explanation of some obscure earlier observations of extremely slight but undoubted carotid sinus reflex responses persisting after 'sympathectomy' [e.g. Bacq *et al.* (22)].

CHEMICAL TRANSMISSION. This article is not the place for extensive discussion of chemical transmission problems; the more so as Chapter VII of this *Handbook* by von Euler is devoted to this subject; in addition, several very instructive reviews have been published, such as those of von Euler (207–210) and Holtz (129). Only a few words will be said about the chemical transmitter at the vasoconstrictor nerve terminals.

Norepinephrine is considered to be the main transmitter at postganglionic adrenergic nerve terminals. As regards the vasoconstrictor nerve terminals, however, the evidence that norepinephrine is the transmitter is indirect and rests chiefly on our knowledge of the vascular effects of norepinephrine and epinephrine.

Epinephrine and norepinephrine both have a pure vasoconstrictor action on some vessels, e.g. those of the skin and intestines. In skeletal muscle vessels epinephrine has a dual action. In low concentrations it has a vasodilator, in higher concentrations a vasoconstrictor, action. Under the influence of sympatholytic drugs, such as ergotamine, the vasoconstrictor action is blocked and even high doses of epinephrine produce vasodilatation. Norepinephrine, on the other hand, has a purely constrictor effect even on skeletal muscle vessels. Its vasoconstrictor effect is completely blocked by sympatholytic drugs without any vasodilator action emerging, as shown by Hartman (114), Clark (59), Folkow *et al.* (83) and Youmans *et al.* (230).

Folkow & Uvnäs (90, 91) presented experiments on cats to show that the transmitter liberated by vasoconstrictor reflexes was devoid of a vasodilator action on blood vessels. In contrast to the constrictor effect of epinephrine, but in common with that of norepinephrine, the action of the vasoconstrictor transmitter could be completely blocked but not reversed by sympatholytic drugs. Hence the transmitter could not plausibly be identified with epinephrine, but was probably norepinephrine. The observation by Schmiterlöw (190) that the arterial walls contain almost solely norepinephrine is consistent with such an assumption.

In the opinion of Lundholm (158) the vasodilator effect of epinephrine is secondary to lactic acid production caused by epinephrine in the muscles. The vasodilatation is thought to be produced by the accumulated lactic acid. It should be borne in mind, however, that conclusions as to the chemical nature of the transmitter substance which are based on observations of its vascular effects after intravenous or intra-arterial administration do not possess any major evidential value. In contrast to intravascularly administered epinephrine, the epinephrine which, under physiologic conditions, is liberated at the vasoconstrictor nerve terminals, does not diffuse into the surrounding skeletal muscle but probably has merely a local action round the site of the neuroeffector junction. Such a local vascular effect of epinephrine might well be exclusively vasoconstrictor. [For further information, see Folkow *et al.* (83) and von Euler (210).]

The chemical transmission at the coronary vasoconstrictor nerve terminals has been the subject of extensive discussion. Since both epinephrine and norepinephrine given intravascularly lead to an increased coronary blood flow, it has been considered that they cannot be transmitter substances at vasoconstrictor nerve terminals. It has consequently been repeatedly hypothesized that the coronary vessels are supplied by parasympathetic vasoconstrictor nerves with acetylcholine as transmitter [Anrep & Segall (17), Gollwitzer-Meier & Krüger (101), Essex *et al.* (79), Gregg & Shipley (110)]. Since both epinephrine and norepinephrine, on intravascular administration, produce a substantially increased myocardial activity which is known to lead to an elevated coronary flow, it is possible although not proved that norepinephrine might have a purely constrictor effect if it could be injected locally into the coronary wall muscle without diffusing into the cardiac tissue.

Several authors, such as Greene (108), asserted that the vagus nerves contain adrenergic fibers to the heart. In addition to accelerator fibers the vagal adrenergic outflow might contain coronary constrictor fibers, as suggested by Greene. Acetylcholine has a marked vasodilator action on the coronary vessels, according to Folkow *et al.* (84), and cannot serve as a constrictor mediator. It is plausible, therefore, to assume for the time being that norepinephrine or (less probably) epinephrine is the transmitter at the coronary constrictor nerve endings. The coronary

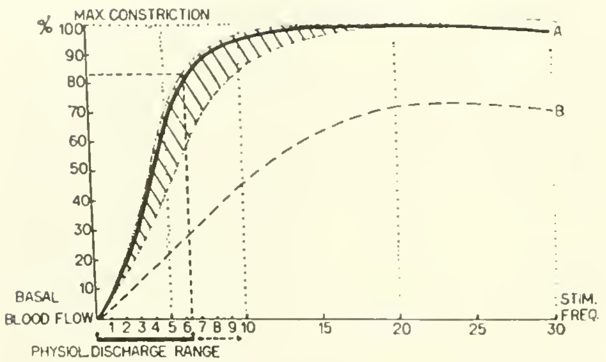

FIG. 2. The correlation between stimulation rate and constrictor response in about 40 experiments. The spread between the different experiments indicated by the traced surface. *A* represents the average of 10 experiments where the constrictor responses were especially marked. *B* indicates how the correlation between constrictor response and stimulation rate is changed when vascular tone is reduced by vasodilator drugs. [From Folkow (80).]

innervation is further discussed by Gregg (109), Folkow *et al.* (81) and von Euler (210).

PHYSIOLOGIC PROPERTIES AND IMPULSE FREQUENCY. The preganglionic fibers are regarded as myelinated B fibers, and the postganglionic as nonmedulated C fibers. According to Maltesos & Schneider (160) there is a not inconsiderable variation in fiber diameters. On stimulation of vasoconstrictor fibers in the sympathetic chain of dogs, the distribution of the threshold values showed a tendency to accumulate around certain values suggestive of a grouping around certain fiber diameters.

Since the vasomotor fibers are of B and C type, they might be expected a priori to show a low firing frequency under physiologic conditions. Available experimental data confirm that this is the case. The series of beautiful experiments conducted by Bronk and co-workers in the 1930's is still the most important contribution that has been made to electrophysiologic data on the central cardiovascular control. Bronk *et al.* (39) determined the transmission rate in postganglionic cardiac fibers to range from 0.6 to 1.5 m per sec. The recorded action potentials varied in magnitude, but not infrequently amounted to 50 μv, a fact indicating a synchronous activity in groups of postganglionic fibers. This grouped activity is discussed in further detail on page 1141. In single fiber preparations from the cervical sympathetic trunk, the authors observed impulse frequencies in preganglionic fibers ranging from 1 to 2 up to 10 to 15 per sec., a frequency that was seldom exceeded. Folkow (80), Girling (100), Celander & Folkow (53), Celander (51) and Folkow *et al.* (86) have indirectly reached similar conclusions.

Girling stimulated the cervical sympathetic trunk in rabbits and found that the degree of vasoconstriction in the ear was a function of the frequency of the stimulation. The effective range of frequency was from 0.5 to 60 stimuli per sec., with approximately 25 per sec. giving the maximum effect. The relation of resistance to flow was such that a small change of frequency could produce a marked change in the resistance to flow. Girling also noted that the higher the frequency of stimulation and the more pronounced the vasoconstriction, the higher was the critical closing pressure.

Folkow studied the correlation between frequency of stimulation and vasoconstrictor response on stimulating the lumbar sympathetic chain and recording the blood flow in the skeletal muscles of a hind limb in the cat. An increase in frequency of the stimuli from 0 to 6 impulses per sec. resulted in an almost linear rise of the peripheral resistance and a vasoconstriction amounting to 80 to 85 per cent of the maximal effect. Virtually maximal vasoconstriction was obtained at a frequency of stimuli of 10 impulses per sec. (fig. 2). Celander & Folkow (53) observed in cutaneous vessels of the cat that 2 stimuli per sec. already increased the peripheral resistance 15- to 20-fold; between 6 and 10 stimuli per sec. there was a steep rise of the peripheral resistance; the curve then flattened and maximal values of 100-fold were found at a frequency of 15 to 25 per sec. Folkow and co-workers (86) reported a similar hyperbolic relation between the frequency of stimuli and the degree of effector response on stimulation of accelerator fibers to the heart, 90 per cent of the maximal acceleration effect having appeared at 8 to 10 impulses per sec.

Folkow (80) further reported that a reflex vasoconstrictor response elicited by occluding the common carotids in the cat disappeared within 4.5 to 5 sec. after release of the vessels. Vasoconstriction produced by stimuli with frequencies below 6 to 8 per sec. similarly disappeared within 4.5 to 5.5 sec. after cessation of the stimulation. On stimulation with frequencies exceeding 6 to 8 per sec., the latent period for abolition of the vasoconstriction increased; Folkow attributed this to a local accumulation of abnormally large amounts of vasoconstrictor transmitter substance which took longer to be eliminated at the nerve terminals at these excessively high impulse frequencies. Since an impulse frequency of 6 to 8 per sec. is the

highest that fails to produce any abnormal post-stimulatory prolongation of the vasoconstrictor responses, Folkow concluded that the physiologically occurring peripheral vasomotor discharge rate exceeded 6 to 8 impulses per sec. only in exceptional cases.

The direct recordings of Bronk *et al.* are strikingly consistent with the indirect observations made by Folkow *et al.* and Girling. Maximal effects of stimulation may appear at impulse frequencies of around 10 per sec. and normal effector activity maintained with 1 to 3 impulses per sec., although this may require supramaximal stimulation and simultaneous discharge of all postganglionic fibers.

The fact that all blood vessels have a vasoconstrictor innervation does not mean that vasoconstrictor tone is evenly distributed in the various vascular beds. The general opinion is that this tone is especially pronounced in the splanchnic vessels, but its existence in cutaneous and muscle vessels is evident from the simple fact that the blood flow increases considerably in those vascular areas with sympathectomy. In other vascular areas, such as the cerebral region, vasoconstrictor tone is considered to be slight.

It is not known whether the varying degrees of tone in different vascular areas may be due to varying frequencies of the vasoconstrictor discharge thereto or to other factors. Celander & Folkow (53) have pointed out that quantitative differences in the vasoconstrictor innervation apparently exist between, for instance, cutaneous and muscle vessels. Stimulation of the abdominal sympathetic chain increased the peripheral resistance 9.5 to 10 times in the muscle vessels, but up to 100 in the cutaneous vessels. In the opinion of Celander & Folkow, these quantitative differences in the responses were probably due to a more abundant vasoconstrictor innervation to the cutaneous than to the muscle vessels.

Sympathetic Vasodilator Nerves

Electrical stimulation of sympathetic fibers usually brings about vasoconstriction in the innervated area, even if the stimulated outflow contains both vasoconstrictor and vasodilator fibers, since the action of the former predominates. By special techniques, such as the use of stimuli of certain characteristics and physostigmine, it may be possible to produce a vasodilator effect [Bülbring & Burn (44), Folkow & Uvnäs (90, 91)]. The vasodilatation obtained is, however, usually slight and transient. Better results are yielded by observations on animals treated with ergotamine or other sympatholytic drugs. If the sympathetic outflow contains vasodilator fibers, electrical stimulation is then able to produce manifest vasodilatation, because when the action of the released vasoconstrictor transmitter is blocked that of the vasodilator transmitter is unmasked.

Uvnäs and associates (75, 76, 149, 152) have lately succeeded in activating sympathetic vasodilator nerves in cats and dogs by topical stimulation in the brain, using the Horsley-Clarke technique which allows observations without previous administration of sympathicolytic agents.

PERIPHERAL DISTRIBUTION. *a) Skeletal muscles.* Sympathetic vasodilator nerves were shown to run to the muscles of the hind legs of the dog and cat by Bülbring & Burn (44), Folkow & Uvnäs (90, 91), Frumin *et al.* (93), Youmans *et al.* (230) and possibly of the hare [Bülbring & Burn (47)] and fox (unpublished observations). Other animals, e.g. the rabbit and monkey, were claimed to lack such nerves.

Barcroft and co-workers (25) noted an increase of the human forearm blood flow during fainting. Since the arterial pressure fell at the same time and the blood flow was shown to be greater in a normal forearm than in a nerve-blocked forearm, sympathetically-mediated active vasodilatation was suggested to occur in the normal forearm.

b) Coronary vessels. The sympathetic outflow to the heart is commonly assumed to contain coronary dilator fibers since electrical stimulation of the stellate ganglion or of the cardiac nerves has been observed to cause an increase in the coronary flow [Gollwitzer-Meier & Krüger (101), Greene (108), Katz & Jochim (138), Gregg & Shipley (110), Winbury & Greene (225) and others]. Circumspection is required, however, in the interpretation of these observations, for stimulation of the sympathetics to the heart brings about acceleration and an increase of the contractile force of the heart and hence an increase in the metabolism of the heart muscles. This in itself will increase the coronary blood flow, probably due to the accumulation of metabolites with a vasodilator action. Gregg & Shipley (110) reported that electrical stimulation of the sympathetic nerves to the heart produced an increase in the coronary flow without a concomitant acceleration of the heart. This observation suggests that sympathetic vasodilator fibers run to the coronary vessels. Katz & Jochim (138) are alone in assuming that cholinergic vasodilator fibers to the coronaries run in the vagus. An extreme view is held by Eckenhoff (73) who claims that the coronary

vessels are devoid of nervous regulation. The coronary blood flow would consequently be regulated only by the metabolic need of the heart.

c) Skin. Bülbring & Burn (46) have claimed that, in contrast to other cutaneous areas, the vessels of the ear have a sympathetic vasodilator nerve supply since stimulation of the cervical sympathetic caused a slight increase in the volume of the ear in the ergotaminized dog. Folkow and co-workers (82), however, also stimulating the cervical sympathetics, were unable to convert a vasoconstrictor response in the ear into a vasodilator response, even with the use of huge doses of ergotamine or Dibenamine. A possible explanation of the divergent results is the different techniques used for recording the blood flow. Uvnäs *et al.* measured the venous outflow from the distal part of the ear while the plethysmographic technique of Bülbring & Burn revealed volume changes not only in cutaneous areas but also in the muscles at the base of the ear.

d) Intestines. The assumption that the splanchnic nerves carry vasodilator fibers to the intestines of the dog and cat is based on the observation of Bülbring & Burn (46) that stimulation of a splanchnic nerve causes an increase in the volume of an intestinal loop enclosed in a plethysmograph. Folkow *et al.* (83) confirmed that stimulation of a splanchnic nerve was able to induce a slight increase of the intestinal venous outflow in an ergotaminized cat. The latter writers attributed the increase in blood flow not to activation of vasodilator nerves, but to changes in the peripheral vascular resistance caused by relaxation of intestinal muscle.

From the available experimental evidence discussed above, Uvnäs *et al.* concluded that a sympathetic vasodilator supply in the dog and cat was present in the striated muscles and possibly the heart, but not in the intestines and the skin. Figure 10 illustrates the present writer's view of the central and the peripheral distribution of the sympathetic vasodilator outflow.

Cannon *et al.* (48) recently questioned whether all vasodilator effects observed on activation of the sympathetic nerves might not be due to a decrease of vasoconstrictor tone since direct stimulation and reflex activation of the sympathetic outflow might sometimes be accompanied by poststimulatory inhibition of the tonic discharge in postganglionic fibers. A similar poststimulatory inhibition was observed by Bronk *et al.* in the inferior cardiac nerves after hypothalamic stimulation. The observations are interesting, but their physiologic implications are quite unknown.

The occurrence of poststimulatory inhibition of the tonic sympathetic cardiovascular discharge does not warrant the assumption that no vasodilator nerves exist. It is not possible, for instance, to class as poststimulatory inhibition those vasodilator responses in skeletal muscle to intracerebral stimulation that are potentiated by physostigmine and completely abolished by atropine, or that can be elicited by postganglionic stimulation after degeneration of preganglionic fibers.

CHEMICAL TRANSMISSION. *a) Skeletal muscles.* As long as all sympathetic postganglionic neurons were believed to be adrenergic and epinephrine to be the sole transmitter substance at sympathetic postganglionic nerve terminals, it was logical to assume that epinephrine was also the transmitter at sympathetic vasomotor nerve terminals, both vasoconstrictor and vasodilator. After the discovery of cholinergic fibers in the sympathetic postganglionic outflow [Dale & Feldberg (78)], it was not surprising, however, to learn that in the dog the sympathetic vasodilator nerves to facial muscles [von Euler & Gaddum (211)] and to muscles of the hind legs [Bülbring & Burn (44)] were regarded as cholinergic. These claims were based on the fact that in both areas stimulation of the sympathetic nerves caused contractions of muscles deprived of somatic motor innervation. In the hind legs of the dog, the vasodilator effects were augmented by physostigmine and blocked by atropine. Since in the hind legs of the cat, vasodilator responses occurred only in ergotaminized animals and were not significantly influenced by physostigmine and atropine, cat vasodilator fibers were believed to be adrenergic, epinephrine being the chemical mediator.

Following the demonstration by Rosenblueth & Cannon (184) that the abdominal sympathetic nerves contained both adrenergic and cholinergic vasodilator fibers, Bülbring & Burn (45) demonstrated cholingeric vasodilator fibers to the hind legs of the cat since they observed a feeble Sherrington phenomenon in a denervated leg on stimulation of the abdominal sympathetic chain. A similar observation had already been made in 1933 by Hinsey & Cutting (125).

Uvnäs *et al.* (91, 92) reached the conclusion that the sympathetic vasodilator nerves to the skeletal muscles of the cat were exclusively cholinergic since the vasodilator responses in the hind legs to stimulation of the abdominal sympathetic chain and to intracerebral stimulation were potentiated by physo-

stigmine and abolished by atropine, and since acetylcholine appeared in the perfusate from physostigminized legs, as had previously been shown to occur in the dog.

b) Coronary vessels. The sympathetic coronary vasodilator nerves are conventionally assumed to be adrenergic. It is indisputable that epinephrine increases the coronary blood flow, even on intracoronary injection. Moreover, many workers have demonstrated that stimulation of the stellate ganglion or of the cardiac sympathetic nerves increases the coronary output. Atropine does not abolish this effect. However, epinephrine as well as sympathetic stimulation increases the activity of the heart. Consequently, it cannot be ruled out that the increased blood flow may be secondary to the increased muscle metabolism as it is in the skeletal muscle during exercise.

Acetylcholine dilates the coronary arteries [Eckenhoff *et al.* (74), Folkow *et al.* (84), and the sympathetic nerves carry cholinergic fibers to the heart in the cat and dog [Gollwitzer-Meier & Krüger (101), Folkow *et al.* (81)]. These observations suggest that the coronary vasodilator fibers—if such fibers exist—may be cholinergic.

c) Conclusion. No positive evidence has been presented to show that epinephrine is a nervous mediator of vasodilator effects. Until the existence of adrenergic vasodilator fibers has been experimentally established, they are better omitted from the discussion. [This question has been discussed in greater detail by Folkow & Uvnäs (92).]

PHYSIOLOGIC PROPERTIES AND IMPULSE FREQUENCY. No direct observations have been made regarding the diameters and transmission properties of fibers in the sympathetic vasodilator outflow since it has not yet been possible to identify or isolate such fibers. It is plausible by analogy to assign the preganglionic fibers to group B and the postganglionic fibers to group C.

Maltesos & Schneider (160, 161) stimulated the abdominal sympathetic chain in dogs and observed an increased blood flow in the femoral vein. A concentration of the chronaxie values for vasodilatation around figures between 0.1 and 6 msec. was attributed to the presence of vasodilator fibers of varying diameters.

Experimenting on cats, Folkow & Gernandt (85) reported an increased outflow of impulses recorded from fine strands of the peroneal nerve running to the muscles of the hind limb, closely associated in time with the vasodilator effect in the muscle caused by hypothalamic stimulation. This discharge was assumed to reflect the activity in small postganglionic nonmyelinated sympathetic vasodilator fibers. The voltage of the spikes was too low to allow any detailed analysis of the discharge.

Studies on the relation between the impulse frequency and the degree of vasodilatation were carried out by Folkow (80) in the hind-leg muscles of the cat by stimulating the abdominal sympathetic chain after administration of dihydroergotamine to block the vasoconstrictor effects of the stimuli. It was found that dilatation already occurred at a stimulation rate of 1 per sec. With a frequency of 6 per sec. the dilatation was very marked with more than a fivefold increase of the blood flow, while at 12 per sec. a maximal vasodilator response appeared. Atropine completely blocked the vasodilatation, thus proving it to be due to activity in cholinergic vasodilator nerves.

The meager experimental evidence available concerning the physiologic properties of the sympathetic vasodilator nerves accordingly suggests properties resembling those of the vasoconstrictor nerves. The physiologic firing rate can be assumed to be rather low, up to about 10 per sec. As far as is known, no tonic discharge occurs in the sympathetic vasodilator outflow.

Parasympathetic Vasodilator Nerves and Cardiac Vagus

PERIPHERAL DISTRIBUTION. Parasympathetic vasodilator nerves are considered to run in the chorda tympani to the tongue and glands of the oral cavity, and in the sacral autonomic outflow to the genitals and, possibly, to the urinary bladder and rectum. Investigations recently reported by Hilton & Lewis (122–124) show, however, that the vasodilatation observed in the sublingual gland on stimulating the chorda tympani probably is produced by bradykinin formed by the activated gland. There is no need to postulate a separate vasodilator innervation. As regards the tongue, stimulation of efferent fibers in the chorda tympani elicits a very marked increase in the venous outflow. Since this vasodilator effect cannot be ascribed to increased metabolic activity, one has to assume that it is due to activation of vasodilator fibers.

Vasodilator fibers are claimed to run in the facial nerve [Cobb & Lennox (60)] and the trigeminal nerve. The reports on the course and origin of these fibers are unreliable. It is not clear whether they are efferent fibers, or afferent fibers capable of antidromic transmission of vasodilator impulses. Vagal vasodilator fibers are said to supply the liver blood vessels [Ginsburg & Grayson (99)].

CHEMICAL TRANSMISSION. Acetylcholine is believed to be the transmitter at all parasympathetic nerve endings. Bacq (21) found, in conformity with this view, that vasodilatation produced in the canine penis by stimulation of the sacral nerves was potentiated by physostigmine and blocked by atropine. It is worthy of note that vasodilatation elicited in the tongue by stimulation of the chorda tympani [Erici & Uvnäs (78)] is not blocked by atropine. The cause of this resistance to atropine is unknown, and further investigations into the chemical transmission at vasodilator nerve terminals might be well worthwhile.

PHYSIOLOGIC PROPERTIES. Very little is known about the physiologic properties of the parasympathetic vasodilator fibers. Stimulating the lingual nerve of dogs with sinusoidal waves, Maltesos & Schneider (161) found vasodilator fibers with various time constants. The chronaxie values varied between 0.1 and 6 msec. with a tendency to grouping around four values, 0.2, 0.8, 2.3 and 5.5 msec.

The physiologic range of the discharge rate is unknown, but it seems reasonable to assume that the relation between firing frequency and vasodilator effect is about the same for the parasympathetic vasodilator fibers as for the other efferent vasomotor nerves.

Heinbecker & Bishop (115) reported that in the turtle vagus impulses having a negative inotropic effect passed along the fine myelinated B_3 fibers, whereas a negative chronotropic action was obtained on activation of unmyelinated C fibers. In the cat the negative inotropic fibers may be mostly, and the negative chronotropic fibers are always, thin myelinated fibers. The cardiac efferent fibers are thus very fine and their potentials are difficult or impossible to record. Schaefer (188) was occasionally able to see spontaneous volleys of slow impulses of low voltage in B fibers. He observed a rhythmicity in the discharge which, according to him, reflected the effect of the afferent cardiac impulses on the medullary cardiovascular center.

CENTRAL REPRESENTATION OF VASOCONSTRICTOR AND CARDIAC NERVES

Spinal Cord

SPINAL VASOMOTOR TONE. As far back as 1864, Goltz (102) demonstrated convincingly that nervous vasoconstrictor tone was present in a spinal animal. The nervous structures responsible for this tonic discharge are located in the lateral horn.

Govaerts (103–105) and Alexander (6) reported direct recording of the activity in the sympathetic cardiac outflow of spinal animals. Both of them found a persisting discharge after section of the buffer nerves (the sinus and vagus nerves). A surprising observation was Alexander's finding that a continuous discharge still occurred in the inferior cardiac nerve fibers after total deafferentation of the thoracic spinal cord. The cord was transected in the lower cervical and midthoracic regions. In addition, all afferent fibers to the isolated thoracic part of the cord were cut. The tonic activity of this spinal preparation was fairly slight but unquestionable. It was depressed by hyperventilation or by ventilation with a mixture of 90 per cent oxygen and 10 per cent carbon dioxide, and stimulated by asphyxiation or ventilation with pure nitrogen. Alexander therefore suggested that even in the normal animal the oxygen tension may contribute to the excitatory states of the spinal cardiovascular centers and thereby reinforce the buffer reflexes that are integrated at higher levels of the nervous system. This idea is at variance with the commonly accepted notion that the carbon dioxide tension is the main local chemical factor exciting the vasomotor centers.

SPINAL VASOMOTOR REFLEXES. Numerous workers have observed segmental and intersegmental vasomotor reflexes in both acute and chronic spinal animals. Brooks (43) observed increments of arterial pressure and heart rate while Downman & McSwiney (72) found pressor responses to nociceptive stimuli in the acute spinal cat.

In spinal man, Gilliatt and co-workers (98) observed that deep inspiration elicits vasoconstriction in the fingers both in intact subjects and in patients with a complete break in the functional continuity of the spinal cord above the level of the sympathetic outflow to the hands. Distention of the urinary bladder similarly elicited vasoconstriction in the fingers.

Increase of the arterial pressure in the spinal dog results in an increase of the volume of the spleen [Heymans *et al.* (119)]. Heating of an extremity in spinal monkeys was reported to elicit cutaneous vasodilatation contralaterally [Fulton (94)]. Since the abdominal viscera and the skin of the animals observed have no centrally controlled vasodilator nerve outflow (see p. 1136), the observations point to the presence of vasoconstrictor inhibition in the spinal animals.

The examples adduced above show that the spinal cardiovascular neurons are capable of maintaining a tonic discharge even when all communications with supramedullary regions have been severed and of responding to afferent impulses with segmental and intrasegmental adjustments of the vasoconstrictor tone.

The extent to which spinal vasomotor reflexes are active within the intact organism, with its dominant supramedullary influences, is unknown. However, spinal viscerocutaneous reflexes have been observed both in intact animals and intact human beings. Kuntz (142) observed vasodilatation and vasoconstriction, respectively, in the small intestine of unanesthetized white rats on heating and cooling of the caudal half of the thoracic region. Viscerocutaneous vasoconstrictor reflexes can be elicited in man [Adams-Ray *et al.* (1–5)]. Restricted pallor of the abdominal skin occurred on distention of the urinary bladder in cholecystitis, pancreatitis and other infections. Stürup (199) observed localized cutaneous pallor on distention of the esophagus.

DESCENDING SPINAL VASOMOTOR PATHWAYS. Excitatory impulses pass from the medulla oblongata to the spinal vasomotor neurons in the ventrolateral column, inhibitory impulses in the dorsolateral column [Suh *et al.* (200), Chen *et al.* (58), Lim *et al.* (148), Harrison *et al.* (113), Wang & Ranson (218, 219), Alexander (7)]. On the spinal vasomotor neurons there also converge excitatory and inhibitory pathways from suprabulbar levels, including the mesencephalon and the hypothalamus. Such pathways can pass through the medulla oblongata without having synapses there (see p. 1147). The excitatory and inhibitory influences of medullary and supramedullary regions on the spinal vasomotor neurons will be discussed in greater detail on page 1141.

Medulla Oblongata

HISTORY AND NOMENCLATURE. As was first recognized by Dittmar (64), Owsjannikow (169) and other members of the Ludwig school in Germany, the integrity of medullary structures is essential for the maintenance of normal cardiovascular tone. As early as 1901, Bayliss (26–28) introduced his dualistic vasomotor center theory, according to which the vasomotor tone was governed by the activity of two medullary centers, a vasoconstrictor and a vasodilator center, acting reciprocally. These two centers were thought to be tonically active, the former governing a vasoconstrictor and the latter a vasodilator nerve outflow. Bayliss' theory, which was further elaborated in a monograph of 1923 (29), dominated scientific discussion for several decades. Even though Bayliss' argumentation has been fully confuted by later experimental observations, several authors of textbooks and manuals still subscribe to his theory.

In the second and third decades of this century a number of investigators by exploratory topical stimulation of the medulla oblongata charted some more or less limited regions at the base of the fourth ventricle which were found to be more responsive than other portions of this structure. Regions which on stimulation produced rises or falls of arterial pressure were assumed, in conformity with Bayliss' theory, to constitute the postulated vasoconstrictor and vasodilator centers [Ranson & Billingsley (180), Scott & Roberts (193) and several others].

Experimental evidence available today, as will be discussed in the following, suggests that the medullary control of vasomotor tone is effected solely via variations in the vasoconstrictor discharge and not via alterations in vasodilator nerve activity. Modern authors speak of medullary pressor and depressor regions in order to make clear that they affect the vasoconstrictor tone and hence the arterial pressure by excitation and inhibition, respectively, of the spinal vasoconstrictor neurons.

LOCATION OF PRESSOR AND DEPRESSOR REGIONS. Exploratory stimulation of the medulla oblongata with the Horsley-Clarke technique has shown that the pressor region comprises an extensive zone within the lateral reticular formation, with its principal extension in the rostral two thirds of the bulb. A depressor area is localized to the medial reticular formation and extends chiefly into the caudal third of the bulb [Suh *et al.* (200), Chen *et al.* (58), Monnier (164), Wang & Ranson (218, 219), Alexander (7), Bach (20)].

TONIC ACTIVITY OF PRESSOR AND DEPRESSOR REGIONS. The importance of the medullary pressor area for tonic cardiovascular discharge was demonstrated with an electrophysiologic technique by Alexander (7). In chloralosed or decerebrate cats he recorded a continuous discharge in the inferior cardiac nerves and in the cervical sympathetic (fig. 3*A*, *Section I*). Transection of the medulla oblongata just rostral to the obex, a procedure which cut off most of the pressor area from its descending connections but left the depressor area more or less intact, produced an equivalent reduction in arterial pressure and in cardio-

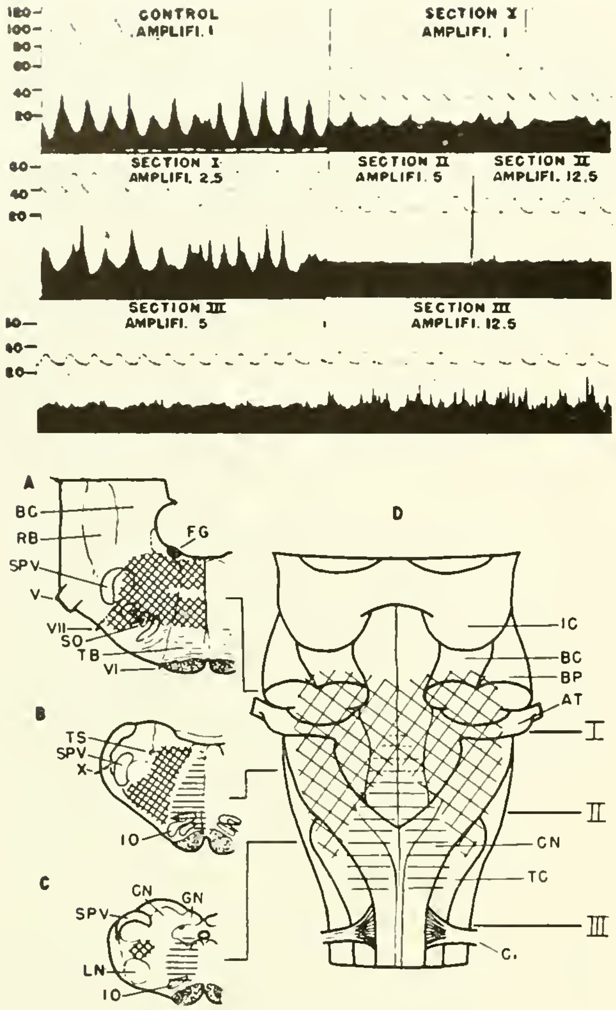

FIG. 3. *A (upper)*: Arterial pressure and tonic activity in the inferior cardiac nerve of an unanesthetized decerebrate and decerebellate cat. Sections indicated refer to transections of the brain stem at the levels shown in part *D* of fig. 3*B*. Amount of amplification of nerve potentials indicated relative to control level. Scales at *left* give arterial pressure in mm Hg. Time signal in all recordings gives 0.2 sec. intervals. [From Alexander (7). *B (lower)*: Localization of pressor and depressor centers in the brain stem of the cat. Pressor regions indicated by *cross hatching*; depressor regions by *horizontal ruling*. *A to C:* Cross sections through the medulla at levels indicated by *guide lines* (*I* to *III*) in *D*. *D:* Semidiagrammatic projection of pressor and depressor regions onto the dorsal surface of the brain stem viewed with the cerebellar peduncles cut across and the cerebellum removed. *AT*, auditory tubercle; *BC*, brachium conjunctivum; *BP*, brachium pontis; C_1, first cervical nerve; *CN*, cuneate nucleus; *FG*, facial genu; *GN*, gracile nucleus; *IC*, inferior colliculus; *IO*, inferior olivary nucleus; *LN*, lateral reticular nucleus; *RB*, restiform body; *SO*, superior olivary nucleus; *SPV*, spinal trigeminal tract; *TB*, trapezoid body; *TC*, tuberculum cinereum; *TS*, tractus solitarius; *V*, *VI*, *VII*, and *X*, corresponding cranial nerves; *I*, *II*, and *III*, levels of transection. [From Alexander (7).]

accelerator tonic discharge in the inferior cardiac nerves (fig. 3*A*, *Section II*).

Alexander further showed that the depressor area, too, probably is tonically active, exhibiting a continuous inhibitory influence on the spinal cardiovascular neurons. Transection at the level of C 1, secondary to the above-mentioned transection just above the obex, resulted in an increased tonic discharge in the inferior cardiac fibers, indicating a release from a tonic inhibitory influence (fig. 3*A*, *Section III*).

If Alexander's observations are correctly interpreted, we should thus have a steady stream of excitatory impulses from the pressor area and inhibitory impulses from the depressor area, bombarding the spinal vasoconstrictor neurons. The intensity of the spinal cardiovascular tonic discharge would accordingly be the result of the balance between these excitatory and inhibitory medullary discharges projecting on the final common path—the preganglionic vasoconstrictor neuron. This hypothesis has the advantage of being rather simple and therefore attractive, but it needs experimental confirmation.

According to Lim *et al.* (148) the influences of the pressor and depressor areas are not confined solely to the spinal vasomotor neurons. They speak of a myelencephalic excitatory and a myelencephalic inhibitory center with excitatory and inhibitory influences on all spinal sympathetic preganglionic neurons [Suh *et al.* (200), Chen *et al.* (55–58), Lim *et al.* (148), Harrison *et al.* (113), Wang & Ranson (218, 219), Alexander (7)].

MEDULLARY CARDIAC CENTERS. Ever since the pioneering investigations of Hunt (130), the heart rate has been considered to be controlled by the tonic and reciprocal actions of two medullary centers, one acceleratory and the other inhibitory. The acceleratory center is thought to be located in those reticular structures that include the pressor center, but its exact localization is unknown. The inhibitory center is believed to lie in communication with the vagal nucleus or amygdaloid nucleus. The efferent accelerator impulses run in the sympathetic outflow, the inhibitory impulses in vagal fibers. In principle, the medullary control of cardiac activity is considered to be organized like the vasomotor control, although with the difference that the cardiac control possesses an efferent parasympathetic inhibitory pathway, the vagus.

Investigations of recent years have established that parallel with accelerating fibers there are fibers in the

sympathetic outflow that selectively influence the contractile force of the heart muscle. Stimulation of such fibers increases the contractile force without necessarily increasing the heart rate [Anzola & Rushmer (18), Randall & Rohse (179), Rushmer (185)]. The central control of these inotropic fibers to the heart has not yet been subjected to detailed studies, but their significance in the regulation of cardiac activity is evident. Interesting papers are to be expected in this new experimental field.

FREQUENCY AND RHYTHMICITY OF MEDULLARY DISCHARGE. The tonic discharge in the thoracic cardiovascular outflow was found to have a frequency of about 2 to 3 per sec. [Bronk *et al.* (39)]. During asphyxia the frequency was observed to increase up to 10 to 15 per sec., a frequency which allows a maximal vasoconstrictor and cardioaccelerator response (see p. 1146).

The preganglionic—and consequently the postganglionic—firing showed a marked grouping in volleys. Since the volleys were bilaterally synchronous, they must have been due to a rhythmic outburst of impulses from the centers. The rhythm frequently was synchronous with the pulse and respiration. The latter two forms of rhythmic cellular activity were shown to be due largely to bursts of impulses from the baroceptors in the carotid sinus and the aortic area, initiated by the systolic rises in pressure, or to impulses from distention receptors in the lungs. It was possible experimentally to drive the cardiovascular centers by repetitive stimulation of the central ends of the carotid sinus or aortic nerves, thus causing the vasomotor nerve cells to discharge periodically with the frequency of the afferent stimulation. Section of the sinus and depressor nerves abolished or reduced markedly the grouped activity of the efferent vasomotor discharge. Recording the splanchnic discharge in cats, Dontas (66) observed rhythmical outbursts of impulses with their maximum occurring after the end of the depressor volleys in the sinus nerve.

The integrity of the medullary vasomotor area is essential for the pressor and depressor reflexes elicited by the specific receptors in the carotid sinus and the aortic arch, and also for similar reflexes elicited by stimulating various afferent nerves [Ranson & Billingsley (180), Alexander (7)]. These vasomotor reflexes as well as the influence of supramedullary regions on the medullary vasomotor centers will be dealt with below.

MEDULLOSPINAL VASOMOTOR PATHWAYS. The excitatory fibers from the pressor region pass to the spinal vasomotor neurons in the ventrolateral column [Lim *et al.* (148), Wang & Ranson (218, 219), Alexander (7)]. Stimulation in the pressor area causes a bilateral increase of the firing in the inferior cardiac nerves but only an ipsilateral increase of the firing in the cervical sympathetics. In fact, there is a contralateral inhibition of the activity in the cervical sympathetics [Alexander (7)]. Since hemisection of the spinal cord considerably reduces but does not abolish pressor responses resulting in ipsilateral hypothalamic or medullary stimulation, partial crossing of the excitatory fibers seems to occur at spinal levels [Harrison *et al.* (113), Wang & Ranson (218, 219)].

The inhibitory fibers from the depressor region pass in the dorsolateral column [Alexander (7)]. These fibers are supposed to cross extensively in the medulla oblongata [Wang & Ranson (218, 219)]. However, further electrophysiologic recordings of the cardiovasomotor discharge and observations on the peripheral vasomotor responses will be necessary to elucidate the functional organization of the bulbospinal excitatory and inhibitory outflows.

MEDULLARY VASOMOTOR REFLEXES. In the carotid sinus and the aortic arch there are localized specialized receptors sensitive to mechanical and chemical stimuli The former receptors, the baroceptors, are stimulated by stretch and are situated in the vascular wall around the bifurcation of the common carotid and in the aortic arch. They react to changes in arterial pressure. The chemoceptors are epithelioid cells concentrated in specialized structures, the carotid and the aortic bodies, which are sensitive to the chemical composition of the arterial blood. Activation of the baro- and chemoceptors elicits depressor and pressor reflexes, respectively.

A detailed discussion of the morphologic and functional properties of the baro- and chemoceptors is beyond the scope of this article. The reader is referred to the numerous reviews on these subjects [Heymans *et al.* (120), Heymans & Bouckaert (118)]. It must suffice here to deal with questions relevant to the medullospinal cardiovascular tonic discharge.

Pressor and depressor reflexes can also be elicited by stimulation of various afferent somatic nerves. These reflexes are mediated, at least in part, via the medulla oblongata.

A substantial flow of afferent impulses from cardiac and pulmonary receptors has been observed in the vagus nerves. These impulses are considered to influ-

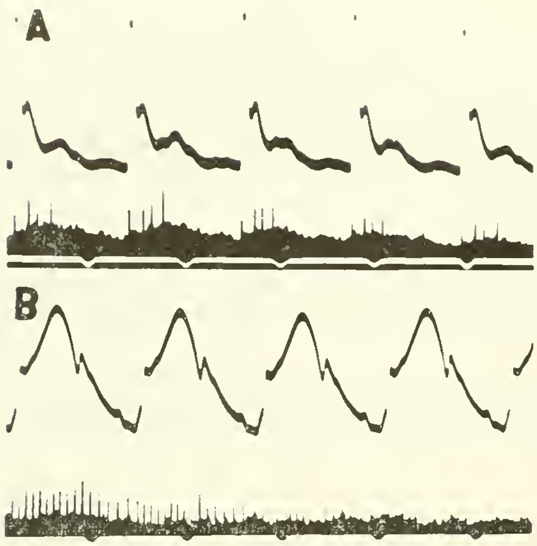

FIG. 4. Afferent impulses from a single pressure receptor in the carotid sinus. The discharge increased when an injection of epinephrine elevated the mean arterial pressure from 55 mm Hg in *A* to 135 mm Hg in *B*. Time: 0.2 sec. [From Bronk & Stella (41).]

ence the spinal cardiovascular discharge via the medulla oblongata, but the physiologic significance of the observations that have been made is still obscure.

a) Baroceptors and baroceptive fibers. The impulse traffic in single baroceptor fibers was first recorded by Bronk & Stella (41, 42) (fig. 4). They observed, at normal arterial pressure levels, a rhythmic impulse discharge with a maximum frequency at the start of systole. The frequency rapidly decreased in the individual volley of impulses and a long resting interval occurred during diastole. As the mean pressure rose, so did the number of active receptors increase, simultaneously with a rise in the frequency of discharge in the individual fiber and a prolongation of the discharge period. At high arterial pressures the receptor discharge was continuous and the rhythmicity less evident. The frequency of discharge rose from a normal level of about 60 impulses to a maximum of 120 to 140 impulses per sec. The baroceptors showed only very slight adaptation to pressure and were insusceptible to variations in the carbon dioxide and oxygen contents of the blood.

References to baroceptor impulses in the sinus nerve usually imply the large spikes that have been recorded from thick afferent fibers. von Euler and co-workers (214) observed in electroneurograms from the sinus nerve not only the large spikes but a number of smaller ones, the frequency of which could be correlated with the pressure in the carotid sinus. By hyperventilation of the experimental animal with pure oxygen, all chemoceptor activity could be made to disappear, but small baroceptor spikes persisted. For quantitative reasons—the small spikes being many times more numerous than the large ones—these authors considered it probable that baroceptor fibers of smaller diameters were of greater significance than the thicker fibers for the sinus depressor reflexes.

Landgren (144, 145) made a more detailed study of the baroceptor potentials in the sinus nerve of the cat and found that the potentials occurred in groups with 10, 40, 50 and 100 per cent of the maximum amplitude. It may be mentioned, by way of comparison, that de Castro (61, 62) found 650 to 700 fibers, all of A type, in sinus nerves from the cat. Of these 3.5 per cent had diameters exceeding 6 to 8 μ; the main group of 79 per cent, diameters of 3 to 5 μ; and 17.5 per cent diameters of 1.5 to 2.8 μ.

Landgren observed that the different receptor fibers had somewhat differing response ranges. The thick fibers were activated by perfusion pressures of between 30 and 200 mm Hg, with a threshold value of 80 to 120 mm Hg for continuous activity. The fine fibers had a somewhat larger response range, with a threshold value of 120 to 150 mm Hg for continuous discharge. The large baroceptor spikes are considered to be produced in stretch receptors acting parallel with the contractile elements, the small ones in receptors which may be in series with these elements. Alternatively the small spikes may be elicited in nerve endings squeezed between the smooth muscle fibers in the media during distention of the wall as well as active contraction of the muscle fibers. For further discussion of this question, reference should be made to the papers of Landgren (144, 145). Figure 5 shows the dependence of the spike heights in a baroceptor preparation on the intrasinusal pressure.

Aortic baroceptive fibers closely resemble in their general properties those of carotid pressure receptors. Their conduction rate is 33 ± 11 m per sec. [as shown by Paintal (170)]. According to Douglas, Ritchie and Schaumann (68–70), not only A fibers but also C fibers occur in the sinus and aortic nerves of the cat and rabbit. Both types of fibers when stimulated produce depressor effects, but the functional significance of the fine depressor fibers is not known; their diameters are too small to permit recording from single fibers.

Bronk and co-workers (39) analyzed the effect of depressor impulses on the frequency of discharge in the sympathetic cardiovascular outflow. Electrical

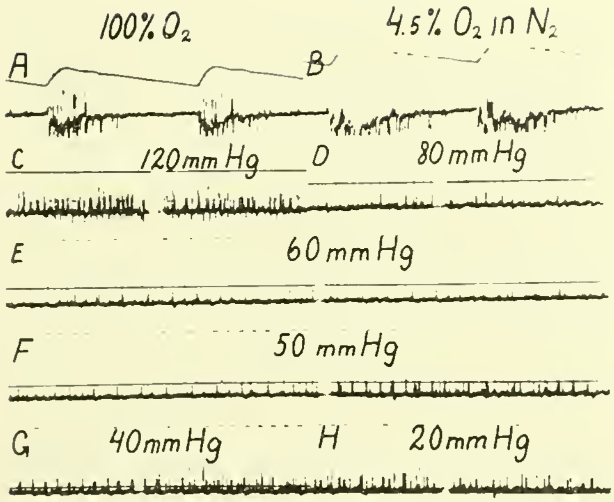

FIG. 5. The impulse activity from a pure carotid sinus baroceptor preparation of the cat. *A:* Control, artificial respiration with 100 per cent O_2. *B:* Control, artificial respiration with 4.5 per cent O_2 in N_2. *C* to *H:* Records of the impulse discharge during a slow pressure decrease (2 mm Hg per sec.). Note the minimum impulse frequency between 60 and 50 mm Hg and the increased discharge below 50 mm Hg. Time: 0.04 sec. [From Landgren (144).]

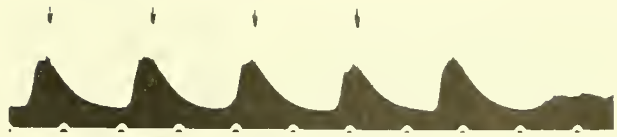

FIG. 6. Rhythmic waves of activity (grouped impulses) recorded in sympathetic cardiac nerve and reflexly driven by stimulating central end of aortic nerve at times indicated by *arrows*. Each wave is associated with the previous stimulus (interval between stimulus and the associated wave, 0.3 sec.). [From Bronk *et al.* (39).]

FIG. 7. Inhibition of efferent sympathetic impulses to the heart by distension of the carotid sinus. *Upper record:* Pressure in the sinus. *Lower record:* Sympathetic impulses. Time: 0.2 sec. [From Bronk *et al.* (40).]

recordings were made from the inferior cardiac nerves and in the cervical sympathetics of the cat. Electrical stimulation of the aortic nerve inhibited continuous firing of the sympathetic. Afferent impulses in the aortic nerve with a frequency of 2 to 15 per sec. caused grouping of the sympathetic discharge (fig. 6). Higher frequencies of the afferent impulses led to a temporary total inhibition of the tonic discharge, followed by escape from the inhibition. Distention of the carotid sinus had the same effect (fig. 7).

Dontas (66) observed that normal splanchnic activity appeared as groups of slowly conducted impulses at the end of each carotid pressor receptor discharge; continuous activity was found less frequently. Splanchnic activity was enhanced by a decrease of pressor receptor inflow.

The observation that afferent inhibitory firing with a suitable frequency is able to produce grouping of the cardiovascular efferent impulses indicates that the normal rhythmic activity of the cardiovascular centers is due to pulsatile volleys of inhibitory impulses originating from, among other sources, the baroceptor areas.

b) Chemoceptors and chemoceptive fibers. The influence of asphyxia on impulse traffic in the sinus nerve was first reported by Heymans & Rijlant (121). Quantitative studies of the relation between oxygen tension, carbon dioxide tension and pH, on the one hand, and the chemoceptor activity on the other, were soon conducted by Bouge & Stella (37), Samaan & Stella (187), Zotterman (231) and others, partly with a technique which allowed perfusion of the carotid sinus under constant pressure but with changes of the chemical composition. It was observed that the chemoceptor discharges in a single fiber increased with an increase of the carbon dioxide tension, with a decrease of the pH and especially with a lowered oxygen tension. Zotterman drew attention to the relatively small height of the chemoceptive spikes, indicating that the chemoceptive fibers belong to the δ group with a transmission rate of 20 to 40 m per sec.

Samaan & Stella (187) observed a chemoceptor discharge also under normal respiratory conditions. It did not disappear until the arterial carbon dioxide tension was 32 to 35 mm Hg or less. von Euler *et al.* (213) also observed chemoceptor impulses under resting conditions in chloralosed cats. The chemoceptors first responded when hemoglobin saturation fell below 96 per cent. The impulse frequency then increased approximately in proportion to the degree of oxygen deficit in the blood. Carbon dioxide was found to elicit chemoceptor activity even at alveolar tensions below 30 mm Hg.

These observations indicate that there may be a chemoceptor bombardment of medullary structures under physiologic conditions. However, since the observations were made on anesthetized animals,

circumspection is required in evaluating the general validity of the results.

Gernandt *et al.* (97) found a pronounced rise of the splanchnic fiber firing in cats during asphyxia and anoxia. Inhalation of pure oxygen decreased the spontaneous activity. After section of all buffer nerves the splanchnic discharge no longer reflected changes of oxygen tension in the blood. On the other hand, an elevation of the carbon dioxide tension in the blood still caused an increase in splanchnic nerve activity. Dontas (66) observed in cats an increase in the splanchnic discharge after injection of chemoceptor activating drugs.

Afferent stimulation of the sinus and vagus nerves has been reported to produce sometimes depressor effects, sometimes pressor effects, the response varying with the parameters of stimuli and the anesthesia [Douglas *et al.* (67)]. Some evidence emerged that there were three groups of efferent fibers, one group of depressor fibers of large diameter, an intermediate group of fine pressor chemoceptor fibers and, lastly, a third group of depressor fibers of small diameter. Neil and co-workers (167, 168) found that stimulation of the carotid sinus nerve in cats elicited a depressor response if the animals were under chloral hydrate or pentobarbital or were decerebrate, but that the response was mainly pressor in animals under chloralose.

The well-known pressor response to occlusion of the common carotids has usually been attributed to the abrupt reduction of arterial pressure in the occluded sinus region, the subsequent reduction of the baroceptor activity and the consequent increase in vasoconstrictor discharge. von Euler & Liljestrand (212) have been more or less alone in their opinion that the pressor response to carotid occlusion is due to activation of the chemoceptors since this response was dependent on the oxygen tension in the arterial blood. During inhalation of pure oxygen the pressor responses virtually disappeared. Landgren & Neil (146) found in cats that the electrical activity in the chemoceptor fibers from the carotid body increases during the pressor response to occlusion of the common carotids but not if oxygen is inhaled.

The activity of the aortic chemoceptors has been described by Landgren & Neil (147). The conduction rate of chemoceptive fibers was reported by Paintal (172) to be 10 ± 2 m per sec.

c) Cardiac and pulmonary receptors and afferent fibers. As was first shown by von Bezold (41, 205), von Bezold & Hirt (206) and Jarisch (132), injection of mistletoe extracts and veratrum alkaloids produces a reflex fall of arterial pressure and heart rate. Several identical or similar cardiovascular reflexes produced by a number of drugs arise from the heart and lungs. The afferent impulses run in the vagus nerves, but the fibers mediating these impulses have so far not been identified with certainty, which is not surprising since it seems very probable that the fibers are small in diameter and hence difficult to record from. Anatomical studies of the cardiac branches of the vagi consistently show that there are few if any fibers above 10 μ in diameter and that the numbers rapidly increase with decreasing fiber diameter. Probably there are also a large number of unmyelinated fibers.

If we except aortic baroceptive and chemoceptive fibers, there are among the cardiovascular afferent fibers, according to Whitteridge (222), the following groups.

1) Afferent fibers from venous side, type A. These fibers, first described by Amann & Schaefer (13), have been related to the cardiac cycle and to the pressure waves in the venous pulse. Each of the three pressure waves, *a*, *c*, *v*, in the venous pressure curve may be accompanied by a volley of impulses [Walsh & Whitteridge (216), Jarisch & Zotterman (133), Schaefer (188)]. There is a linear relation between pressure and impulse frequency. Due to the fairly rapid adaptation rate the receptors corresponding to the A fibers are believed to respond to rises of pressure but not to the absolute level of pressure in the atrium [Struppler (198)]. They behave as if they lie in series with the muscle fibers. They undoubtedly arise from the atria at the openings of the great veins [Jarisch & Zotterman (133), Paintal (170)]. Their conduction rate is 20 ± 5 m per sec.

2) Venous fibers, type B. These fibers show a late systolic volley roughly related to the *v* wave. They arise from endings in the atrial walls; their conduction rate is 13 ± 5 m per sec. [Paintal (170)]. Their behavior suggests that they lie parallel with the atrial muscle fibers.

3) Small fibers. These fibers can be excited by pinching the ventricles and are probably stimulated by veratrin, according to Jarisch & Zotterman (133).

Fibers with a brief discharge during the isometric contraction phase only, perhaps arising in the ventricles or septum, were detected by Whitteridge (221), Dickinson (63) and Pearce (173). Paintal (171) observed in the cat fibers firing in response to phenyldiguanide. Their conduction rate was 6 m per sec.

So far no analysis has been made with an electrophysiologic technique of the efferent cardiovascular discharge patterns accompanying the Bezold-Jarisch

reflex or other cardiovascular reflexes produced by various drugs. The influence of the vagal afferent impulse traffic on the cardiovascular efferent discharge, and the physiologic significance of this traffic, are quite unknown.

d) Other receptors and afferent fibers. The ability of sensory and nociceptive impulses to influence the cardiovascular discharge is demonstrated by the fact that stimulation of afferent nerves, as the sciatic, brachial or trigeminal nerve, produces pressor or depressor effects, depending on the parameters of the stimuli, the depth and nature of narcosis, and other related factors. These reflexes are, according to some authors, at least partly relayed through the medulla oblongata. Alexander (7) observed volleys of impulses in the inferior cardiac nerves in response to single shocks applied to the central end of the sciatic nerve. Repetitive stimulation of the sciatic nerve elicited a pressor reflex and a considerably increased discharge in the inferior cardiac nerves. Transection in the medulla oblongata just below the pressor area (see p. 1139) completely abolished the reflex cardiovascular discharge as well as the pressor reflex.

e) Cardiovascular responses. The cardiovascular response pattern associated with different pressor and depressor reflexes has been incompletely elucidated.

The fall of arterial pressure attending activation of the baroceptors, at all events those in the carotid sinus region, is due partly to bradycardia and partly to peripheral vasodilatation. The principal factor here is the vasodilatation, which is reported chiefly to affect the visceral region but also occurs in muscles and skin [Folkow *et al.* (89), Frumin *et al.* (93), Lindgren & Uvnäs (153, 154)]. Since vasodilatation is due to inhibition of vasoconstrictor tone, it is probable, though not experimentally verified, that vasodilatation affects different vascular regions in inverse proportion to their vasoconstrictor tone.

Bernthal (31) is one of the few investigators who has studied the reflex vasomotor reactions which attend changes of the chemical milieu in a perfused carotid sinus. Anoxia, cyanide, hypercapnia and lactic acid caused pressor reactions with bradycardia and reflex vasoconstriction in a foreleg. Since an increase of the normal oxygen tension and a decrease of the normal carbon dioxide tension in the perfusion fluid resulted in vasodilatation, his findings accord with the supposition of von Euler *et al.* (213) that the chemoceptors are already activated at the oxygen and carbon dioxide tensions which occur under physiologic conditions.

Although the pressor effect of anoxia is usually accompanied by cardiac acceleration, there is very little experimental evidence as to the heart rate response to a chemoceptor stimulus. Heymans & Bouckaert (118) reported that injection of nicotine and cyanide into the carotid sinus produced pressor responses with bradycardia. Bernthal *et al.* (32) observed that chemoceptor reflexes capable of producing pressor reflexes caused not tachycardia, but bradycardia. In these experiments the pressor responses were blocked by a compensation device. The bradycardia, therefore, could not be ascribed to a reflex produced by the arterial pressure rise. Neil (166), believing results more applicable to systemic anoxic conditions could be obtained with chemoceptor impulses bombarding an anoxic medulla rather than, as in experiments of Bernthal *et al.*, an adequately oxygenated medulla, found that such systemic anoxia produced tachycardia and hypertension. However, when both carotid sinuses were then perfused with adequately oxygenated blood, the hyperpnea and hypertension were reduced but the tachycardia persisted. It thus seems as if chemoceptor reflexes produce an increase of vasoconstrictor discharges but no cardiac acceleration.

The reflex vasoconstriction due to excitation of chemoceptors probably concerns all vascular fields, although quantitative differences may exist. Bernthal & Schwind (34) claim that excitation of chemoceptors by anoxia causes more marked vasoconstriction in the limbs than in the intestines. Folkow & Uvnäs (90, 91) reported the chemoceptor-induced pressor responses to occlusion of the common carotids to be due to marked vasoconstriction in both the skeletal muscles and the splanchnic region.

As to the cardiovascular response pattern associated with depressor and pressor reflexes due to afferent impulses in sensory nerves, satisfactory information is still lacking.

f) Efferent pathways. The bradycardia attending the sinus depressor reflex has been shown to be due to the combined action of vagal activation and sympathetic inhibition, vagal activity being most marked immediately following sinus distention, while the slowing due to sympathetic inhibition appeared slowly and became the major restraining influence as the vagal effect diminished [Wang & Borison (217)]. There have been no similar investigations on the role played by the vagal and sympathetic innervation of the heart in pressor reflexes.

All observations—both those made with modern electrophysiologic techniques and those made with more classical methods for determination of arterial

pressure or peripheral blood flow—are consistent in showing that medullary vasomotor reflexes are effected through variations in vasoconstrictor tone. Vasodilatation coincides with a decreased vasoconstrictor discharge; vasoconstriction, with an increased discharge. The question whether vasodilator nerves also take part in medullary vasomotor reflexes has been extensively discussed in past years. Until the 1930's it was generally assumed, in accordance with Bayliss' (29) view, that the medulla oblongata had two vasomotor centers, a vasoconstrictor and a vasodilator center. These two centers had an inhibitory effect on each other. Vasodilator impulses were thought to pass from the vasodilator center (see p. 1155), partly via parasympathetic vasodilator fibers and partly via dorsal root dilator fibers. Increasing numbers of investigators have reported, however, that sympathectomy completely abolishes reflex vasomotor responses [Jarisch (131), Bacq *et al.* (23), Schneider (191), Thomas & Brooks (201), Wybauw (229), Bacq *et al.* (22) and Downman *et al.* (71)].

Of special interest is a paper by Dole & Morison (65) in which they report they were able to confirm Bayliss' observation that a depressor reflex was sometimes (in 40 per cent of the cases) accompanied by an increase in the volume of a sympathectomized hind limb. However, the increase in volume of the limb remained after total denervation of the limb. Dole & Morison therefore concluded that the vasodilatation sometimes observed after sympathectomy was not of nervous origin.

Folkow & Uvnäs (92) and Lindgren & Uvnäs (153, 154), directly recording the blood flow in skin and skeletal muscle vessels of cat limbs with cross-circulation, so eliminating the disturbing influences of mechanical and humoral factors, found that sympathectomy, acute as well as chronic, invariably abolished all vasoconstrictor and vasodilator responses due to occlusion of the common carotids, stimulation of sinus or depressor nerves, and other factors. Sensory denervation of the limb, on the other hand, did not influence the vasodilator or vasoconstrictor reflexes studied at all.

Frumin *et al.* (93), using a flowmeter, measured the blood flow in the femoral artery of a cross-perfused limb and found that it was greatly increased by depressor reflexes produced in different ways. In some experiments they found a slight persisting vasodilator effect even after sympathectomy. This effect was initially attributed to vasodilator activity in the dorsal roots but was later found to be due to a persisting collateral arterial supply to the cross-perfused leg. If all collaterals were severed, all vasodilator effects disappeared with sympathectomy.

Celander & Folkow (52) demonstrated that parasympathetic vasodilator nerves to the tongue or the splanchnic region were not activated by depressor reflexes. Bernthal and co-workers (33) reported that sympathectomy removed all recognizable chemoreflex vasomotor reactions in the foreleg of the dog even though the dorsal root vasodilator innervation remained intact. They concluded that in most dogs sympathetic fibers constitute the sole efferent pathway for vascular reflexes originating in the carotid body.

On the basis of the experimental evidence we possess today, it is accordingly safe to conclude that medullary vasomotor reflexes are mediated solely via variations in sympathetic vasoconstrictor activity.

INFLUENCE OF CARBON DIOXIDE AND OXYGEN ON SPINAL AND MEDULLARY VASOMOTOR NEURONS. Among chemical factors influencing the spontaneous activity of the medullary and spinal vasomotor neurons, carbon dioxide is known to be of paramount importance. Increased carbon dioxide tension in the blood reinforces, and decreased carbon dioxide tension reduces the activity as shown by recording the electrical activity in sympathetic nerves. In the intact animal, anoxia initially stimulates the vasomotor activity.

Bronk *et al.* (39) observed an increase of firing in the inferior cardiac nerves during anoxia which was regarded as secondary to increased firing in the carotid and aortic chemoceptors. Gernandt *et al.* (97) found that increased carbon dioxide in the blood increased the discharge in the splanchnic nerve both before and after section of the sinus and the vagodepressor nerves. Anoxia led to an increase of the potentials, pure oxygen inhalation to a decrease, but both these effects disappeared after buffer nerve section. These findings indicate that in the intact animal the vasomotor neurons are more sensitive to the carbon dioxide tension but less sensitive to the oxygen tension than are the chemoceptors. The direct effect of anoxia on the nerve cells is thought to be a depressant one [Gellhorn & Lambert (96), Schmidt & Comroe (189)], since after cutting of the buffer nerves anoxia depresses the excitability of the medullary respiratory and vasomotor centers.

Contrary observations have been made by Alexander (6) indicating that anoxia can produce an initial increase in the spontaneous activity of the vasomotor neurons in the deafferented spinal cord. Similarly the excitability of vasomotor neurons in

the medulla and hypothalamus may be increased in anoxia (35, 95). However, further experiments with techniques permitting localization of the oxygen deficiency in the central nervous system specifically are needed.

Mesencephalon

We possess little knowledge of the significance of the mesencephalon in vasoconstrictor nervous activity. Both early investigators, using somewhat primitive techniques, and more recent workers employing the Horsley-Clarke technique have, it is true, observed pressor and depressor responses to stimulation of different mesencephalic regions (12, 116, 136, 202). However, it has often been impossible to decide whether neurons originating in the mesencephalon, or merely fibers passing through it, have been stimulated.

Lindgren (149) published an extensive study on the significance of the mesencephalon in vasomotor control. He found that vasoconstrictor neurons originating from the hypothalamus passed immediately beneath the superior colliculus and probably had junctions there with new mesencephalospinal neurons. This outflow contains vasoconstrictor fibers to the intestines and to the skin, and passes in close anatomic relation to sympathetic vasodilator fibers to the skeletal muscles and to fibers capable of activating the catechol secretion of the adrenals. The fact that vasomotor neurons running directly to spinal levels emanate from the mesencephalon is interesting in principle. It indicates that the mesencephalon is the most caudal integrating relay station for this vasomotor outflow and that it may constitute a previously overlooked integrative region for central vasomotor control.

In the opinion of Ranson and his associates (136, 159, 218, 219), the hypothalamic-medullary efferents have a somewhat diffuse extension in the lateral portions of the tegmentum and in the substantia grisea centralis around the aqueduct. These workers disputed the view that the medial longitudinal bundle, the medial reticular formation and the corticospinal tract were of paramount importance for the transmission of sympathetic impulses from the hypothalamus—a view which was asserted by Beattie *et al.* (30).

Hypothalamus

The integrative activity of the hypothalamus on somatic and vegetative functions is considered to apply even to the cardiovascular apparatus. Pressor and depressor responses to hypothalamic stimulation suggest, it is true, that vasomotor structures are scattered diffusely in the hypothalamic regions [for reviews see Karplus (137), Hess (116, 117), Ranson & Magoun (181)], but they shed little light on the function of these structures.

An integrative function requires neuron synapses in the integrative area. Persisting vasomotor responses to hypothalamic stimulation in chronic decorticate animals show that vasomotor neurons originate in the hypothalamus—a fact that was already observed by Karplus (137) in association with Kreidl.

INFLUENCE ON CARDIOVASCULAR DISCHARGE. Pitts, Bronk and Larrabee (175, 176) reported an exemplary study of the hypothalamic influence upon the tonic cardiovascular discharge. They found that the frequency of discharge in the cardiovascular neurons—recorded in the inferior cardiac nerve and in the cervical sympathetic—was linearly proportional to the frequency of hypothalamic stimulation (fig. 8). The preganglionic discharge amounted to about one impulse per 20 to 25 hypothalamic stimulatory impulses. Unilateral stimulation of the hypothalamus produced bilateral sympathetic discharge. On simultaneous bilateral stimulation of the hypothalamus, an almost arithmetical summation of the peripheral discharge was obtained, the occlusion being minimal.

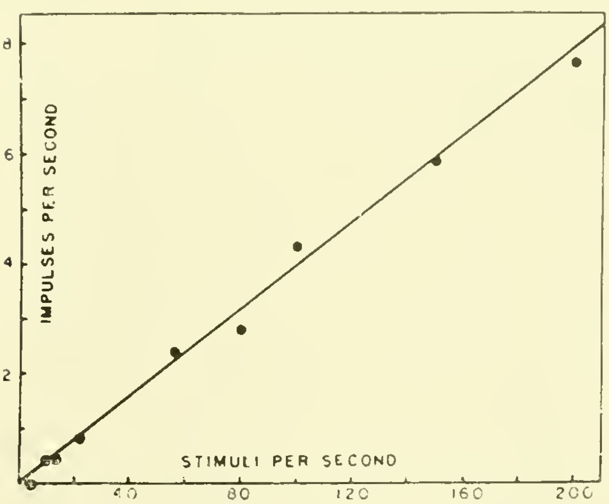

FIG. 8. The relation between frequency of discharge of impulses in a single fiber of the cervical sympathetic nerve and frequency of hypothalamic stimulation. Intensity of stimulation constant. [From Pitts (176).]

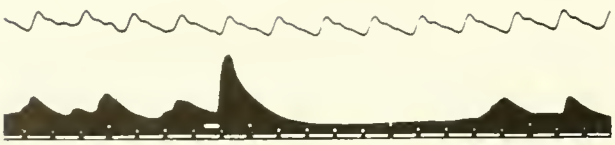

FIG. 9. Inhibition of 'tonic' sympathetic discharge in the inferior cardiac nerve following a short burst of increased activity induced by a brief period of hypothalamic stimulation. *White signal* above *time marker* gives duration of stimulus. No rise of arterial pressure (*upper record*) to account for after-inhibition. Time: 0.2 sec. [From Bronk *et al.* (40).]

The region in which stimulation produced activity in one and the same peripheral neuron was surprisingly large. An approximately constant frequency of discharge was found in the preganglionic neuron, even when the electrode was shifted 3 mm dorsoventrally. In other words, many hypothalamic neurons must converge towards one and the same spinal neuron.

The interference between the hypothalamic impulses, on the one hand, and afferent inhibitory excitatory impulses, on the other, was beautifully demonstrated. On simultaneous hypothalamic stimulation and activation of the baroceptors in the sinus region, the cardiovascular discharge induced via the hypothalamus decreased. Simultaneous stimulation of the hypothalamus and of an afferent nerve with a pressor effect led to a summation of the effects, resulting in an increased cardiovascular discharge. According to Bronk *et al.*, the hypothalamus may play the role of a modifier in the various mechanisms that regulate arterial pressure and heart rate.

A frequency reversal—i.e. conversion of a pressor to a depressor response—on changing from higher to lower frequencies of stimulation was observed by Hare & Geohegan (112) and by Berry *et al.* (36). Bronk *et al.* gave a plausible explanation of such a reversal effect. They observed that with a change-over from high-frequency (20 impulses per sec.) to low-frequency (2 impulses per sec.) stimulation, there was a temporary cessation of the tonic cardiovascular discharge. The result of such interruption of the vasoconstrictor firing will naturally be a fall of arterial pressure.

Characteristic of pressor effects elicited by hypothalamic stimulation is a persisting poststimulatory pressor effect. This has been attributed to a nervous after-discharge [Grinker & Serota (111)], though Bronk *et al.* in no case observed such a discharge; on the contrary, they often found, as mentioned above, a poststimulatory inhibition (fig. 9). The poststimulatory pressor effect is probably attributable to the sluggishness of the peripheral effector organ or, possibly, to catechols secreted from the adrenals. Catechol secretion is often activated by hypothalamic stimulation—a fact that has long been recognized.

Only a few investigators have made any detailed study of the hypothalamically induced peripheral vasomotor reaction patterns. Ström (258) found in the hypothalamus of cats areas which when stimulated electrically produced selective vascular responses in the skin, either constriction or dilatation. Eliasson and his associates (75, 76) were able to localize areas which when stimulated activated the sympathetic vasodilator outflow to the skeletal muscles and, simultaneously, produced cutaneous and intestinal vasoconstriction. Local heating of temperature-regulating areas in the anterior hypothalamus elicits cutaneous vasodilatation [Folkow *et al.* (87, 88)].

HYPOTHALAMICOSPINAL PATHWAYS. The vasodilator effects observed to occur in the skin and intestines on hypothalamic stimulation must be due to inhibition of vasoconstrictor tone since no vasodilator innervation is known to supply these vascular areas. The occurrence of vasoconstrictor inhibition probably means that inhibitory fibers pass from the hypothalamus down to the medullary or spinal vasomotor neurons. The pathways for such inhibitory fibers from the hypothalamus are unknown, although the scattered depressor points found throughout the hypothalamus and mesencephalon indicate the passage of such inhibitory neurons. However, Alexander (7) has suggested that a medial longitudinal depressor band in the rostral part of the medulla oblongata might be a descending inhibitory pathway from the hypothalamus.

Vasoconstrictor neurons pass from the lateral region of the hypothalamus, probably around the aqueduct in the central gray and in the tegmentum mesencephali [Ranson & Magoun (181)].

An interesting question is whether, and if so to what extent, vasomotor neurons emanating from the hypothalamus and other supramedullary regions converge towards the spinal vasomotor neurons and pass the medullary pressor and depressor regions without having any synapses there. It seems probable—not least from the analysis presented by Bronk *et al.*—that some vasomotor neurons, and perhaps the majority, have synapses in the vasomotor centers of the medulla oblongata. Some vasomotor neurons, however, undoubtedly pass outside the medullary vasomotor regions. This applies, for instance, to the

hypothalamic vasoconstrictor-vasodilator pathway that Uvnäs and his associates traced from the hypothalamus, through the mesencephalon and medulla oblongata, down towards spinal levels. It seems plausible to assume that this and other such functional vasomotor units are directly projected to the spinal vasomotor neurons whereby they should have greater possibilities for mediating distinct vasomotor response patterns of supramedullary origin.

Cerebral Cortex

The earlier view that the suprabulbar integrative control of the autonomic nervous system, including that controlling the cardiovascular system, was localized solely in subcortical structures, chiefly the hypothalamus, has gradually been superseded by the opinion that it has an extensive representation in the cerebral cortex. Experimental and clinical data suggest that the cardiovascular medullospinal mechanisms can be influenced from different regions of the cerebral cortex, especially the motor area, the orbital surface of the frontal lobe, the rhinencephalon and the temporal lobe.

Unfortunately these data throw little or no light on the mechanisms through which the cortical control acts. This is partly because only arterial pressure reactions—pressor or depressor responses—generally have been followed, but sometimes cardiac responses—acceleration or retardation—also have been recorded. Moreover, the responses are greatly influenced by various experimental conditions—as for instance the intensity and frequency of stimulation, the type and depth of anesthesia, and the species of animal. Thus, it is not surprising that the experimental findings afford a somewhat kaleidoscopic picture. In virtually no case has an electrophysiologic technique been employed in the study of cortical cardiovascular control.

MOTOR CORTEX. Hoff and Green (107, 126) observed pressor responses and cardiac acceleration on stimulation of the gyrus porcus and the gyrus sigmoideus in the cat, and on stimulation of the cortex adjacent to the superior precentral sulcus as well as scattered points in the trunk and arm areas in monkeys. Depressor responses with or without bradycardia were elicited from various precentrally localized points. They observed a reduction of the renal volume and usually an increase, although sometimes a decrease, of the leg volume. Since these peripheral vasomotor reactions were independent of the changes in arterial pressure, the results show that a peripheral redistribution of the blood flow may be initiated from the cerebral cortex. Similar observations were reported by Lund (157).

Hoff and co-workers (127) observed that bilateral electrical stimulation of foci in the anterior sigmoid gyrus produced, in acute experiments on cats, transient elevations of arterial pressure of 80 to 100 mm Hg together with pronounced renal cortical ischemia. Stimulation of the brain through the intact cranium, in chronic experiments lasting 1 to 6 weeks, caused pathologic changes in the kidneys, presenting the picture of lower nephron nephrosis, presumably due to anoxia caused by the repeated arteriolar constriction. Pronounced arterial pressure rises were observed by Wall & Davis (215) and Kessler (141) in dogs anesthetized with diallyl barbituric acid on stimulation in the sensorimotor cortex. In man and subhuman primates Kennard (139) observed that lesions in the premotor cortex result in alterations of skin temperature and color on the contralateral side of the body. Ablation of the prefrontal cortex of Brodmann's areas 4 and 6 in monkeys has been observed to result in a consistent decrease of the skin temperature on the contralateral side.

FRONTAL LOBES. The frontal lobes have attracted considerable interest in recent years since they have been found probably to exert an inhibitory influence on autonomic functions. Total or partial removal of the frontal lobes in cats and monkeys has been followed by signs of excessive sympathetic activity, e.g. cardiac acceleration, increased release of epinephrine and augmented cutaneous vasoconstrictor reflexes [Kennard (140), Livingston *et al.* (156)]. A depressor pathway has in fact been traced continuously from just behind the frontal pole of the hemisphere as far caudally as the rostral end of the diencephalon and has been regarded as a corticofugal inhibitory pathway [Kabat *et al.* (136)].

Electrical stimulation of the orbital surface has been reported to produce both pressor and depressor reactions [Bailey & Sweet (24), Livingston *et al.* (54, 155, 156), Sachs *et al.* (186)]. The experiments were performed on cats, dogs, monkeys and humans. Ström (197) reported that electrical stimulation of structures in the frontal lobe and the anterior hypothalamus could produce cutaneous vasoconstriction as the sole response. A marked poststimulatory inhibition of the cutaneous vasoconstrictor tone was observed. In the cat the cutaneous vasomotor responses were mainly localized to the pads.

RHINENCEPHALON. Kaada (134) observed two optimum zones in the anterior rhinencephalic areas yielding pressor and depressor responses on electrical stimulation, one in the anterior limbic cortex and a second in the postorbital anterior insula, anterior hippocampal gyrus and neighboring temporal regions in monkeys and in the homologous areas in cats and dogs. Arterial pressure reductions were also produced by stimulation of the amygdaloid and caudate nuclei. Ward (220) stimulated structures in the anterior gyrus cinguli in monkeys and obtained depressor responses with cardiac retardation and in some cases cardiac arrest. Smith (194) in similar experiments had observed pressor responses with or without cardiac acceleration as well as depressor effects, usually associated with more or less pronounced cardiac retardation. In man, too, stimulation of the anterior part of the gyrus cinguli results in alteration of the arterial pressure and pulse rate [Pool & Ransohoff (177)].

Anand & Dua (16) stimulated the gyrus cinguli in conscious cats and monkeys with implanted electrodes. From rostral portions of the gyrus cinguli belonging to the frontal lobe, they usually obtained a rise of arterial pressure, whereas stimulation of caudal parts belonging to the temporal lobe caused a fall. They observed both cardiac acceleration and retardation; but since these did not correlate with the arterial pressure responses, the latter probably were manifestations of variations in vasoconstrictor discharge. Hoffman & Rasmussen (128) observed chiefly depressor responses and inhibition of the gastrointestinal activity on stimulation on the insular cortex in *Macaca mulatta*. Similar effects were obtained on stimulation of the posterior orbital surface and the tip of the temporal lobe. Since the cardiovascular effects persisted after vagotomy, they must be attributed to changes in vasoconstrictor tone.

TEMPORAL LOBE. Stimulation of the human temporal pole has yielded marked rises in arterial pressure [Anand & Dua (14, 15, 16)]. In the monkey, pressor as well as depressor responses have been observed on temporal lobe stimulation [Kaada *et al.* (135)].

EFFERENT PATHWAYS. The pathways for corticofugal excitatory and inhibitory cardiovascular effects are largely unknown. Probably the majority of the corticospinal cardiovascular neurons are relayed in or pass through the hypothalamus. However, some efferent neurons might run outside the hypothalamus. Spiegel & Hunsicker (195) stimulated the cortex of the cat and obtained arterial pressure and bladder responses which persisted after transverse sections in the medulla oblongata that were designed to interrupt pyramidal or extrapyramidal tracts. The conclusion was reached that there exist both pyramidal and extrapyramidal pathways for autonomic efferents. In monkeys and chimpanzees, they found that arterial pressure responses arising from stimulation in the sensory motor cortex were completely abolished by pyramid section, but were uninfluenced by lesions in the hypothalamus. Responses elicited from the posterior orbital surface and anterior insula disappeared after destruction of the hypothalamus. The vasomotor pathways from the temporal lobe, however, were found not to pass the hypothalamus.

The observations of Spiegel & Hunsicker thus suggest that autonomic pathways pass through the hypothalamus from some areas but not from others. However, observations made with such a rough technique as that employed in the above experiments cannot be credited with any major evidential value. It should also be pointed out that corticospinal pathways passing through the hypothalamus may well have a pyramidal or juxtapyramidal course in more caudal regions, as for instance the pons and medulla oblongata. This is the case with the sympathetic vasodilator outflow which in its posthypothalamic course first turns dorsad across the tectum mesencephali and then once more descends ventrad and passes beneath its medullary portion in close relation to the pyramidal pathway. This vasodilator pathway, which is also accompanied by vasoconstrictor fibers, would therefore have been severed in experiments conducted by the methods of Spiegel & Hunsicker.

The pioneering investigations of Magoun *et al.* have demonstrated that the reticular system in the brain stem contains structures which have a facilitatory and inhibitory influence on both reflexogenic and corticogenic somatic motor phenomena. Bach (20) sought to find out whether stimulation of these reticular structures also had inhibitory and facilitatory effects on autonomic responses and whether certain combinations of effects, as for instance inhibition of the patellar reflex with a coincident depressor effect, could be demonstrated; he found that this was not the case. Bach's investigation did not lend weight to the hypothesis which identifies the somatic facilitative and inhibitory reticular formation with vasopressor or vasodepressor structures.

In the opinion of Landau (143), the autonomic

corticospinal pathways serve chiefly to facilitate autonomic response patterns elicited at spinal and peripheral levels. However, available data do not elucidate the efferent pathways by which the vasomotor reactions produced from the cortex are mediated. Yet considering the knowledge we possess of the central representation of the sympathetic vasodilator outflow, it is probable that most, and perhaps virtually all, of the observed vasomotor responses have been produced via variations in vasoconstrictor tone. Of the observations that have been reported, an analysis of the peripheral vascular reaction pattern has been made only by Lund (157) and Green & Hoff (107). These authors stimulated the motor cortex in cats and observed an increase of the leg volume, pointing to vasodilatation there which may have been produced by sympathetic vasodilator activity.

Cerebellum

Occasional early reports suggest that the cerebellum in some way or other influences the central vasomotor control [see Wiggers (223, 224)], but its significance in vascular regulation is not yet clear.

According to Moruzzi (165), stimulation in the vermis cerebelli may inhibit both pressor and depressor reflexes elicited by stimulation of afferent nerves, such as the sciatic, superior laryngeal and central end of the vagus. Spontaneous vasomotor waves of central origin are also inhibited. Moruzzi further demonstrated that pressor reflexes elicited by occlusion of the common carotids or by intracarotid injections of cyanide were inhibited by stimulation of vermian structures with intensities yielding strong inhibition of the decerebrate rigidity. In his view, the inhibition is due to a central effect on bulbopontine centers.

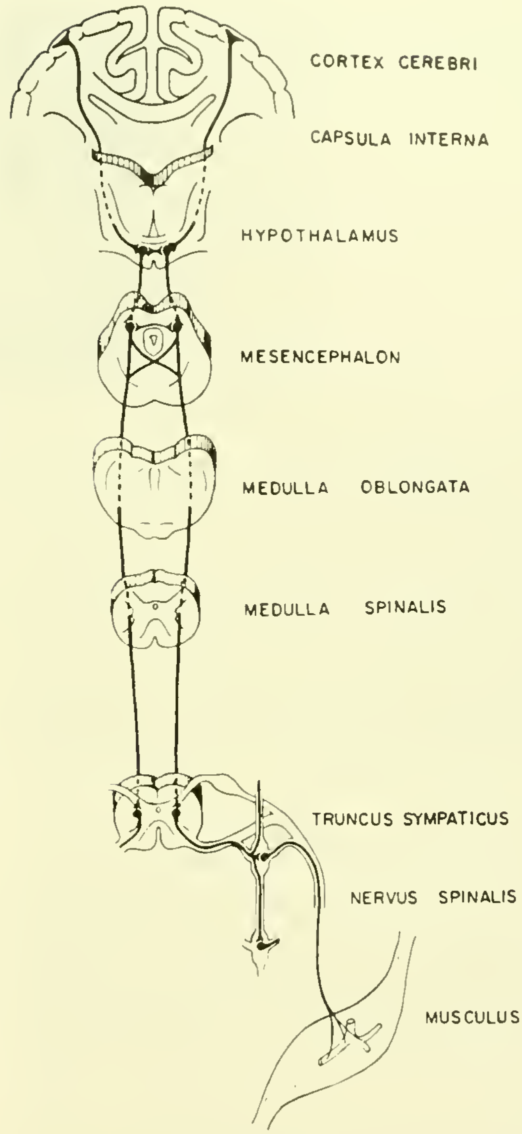

FIG. 10. Schematic drawing showing the central and peripheral course of the sympathetic vasodilator pathways. [From Lindgren (149).]

CENTRAL REPRESENTATION OF SYMPATHETIC VASODILATOR NERVES

In recent years Swedish investigators have been able to activate sympathetic vasodilator nerves to the skeletal muscles in dogs, cats and foxes by intracerebral stimulation. This outflow has been shown to have a widespread intracerebral representation. The corticospinal course of a sympathetic vasodilator tract (fig. 10) has been traced from its cortical origin down to spinal levels by Lindgren *et al.* (150). The vasodilator responses to intracerebral stimulation were completely abolished by small doses of atropine and were augmented by physostigmine (figs. 11, 12). To show that these effects were due to a peripheral action and not to an action on ganglia or intracerebral synapses, cross-perfusion experiments were performed in which it was shown that these drugs blocked and augmented, respectively, the vasodilator responses in the muscles peripherally. It is thus safe to conclude that these vasodilator responses are due to activation of cholinergic sympathetic vasodilator nerves.

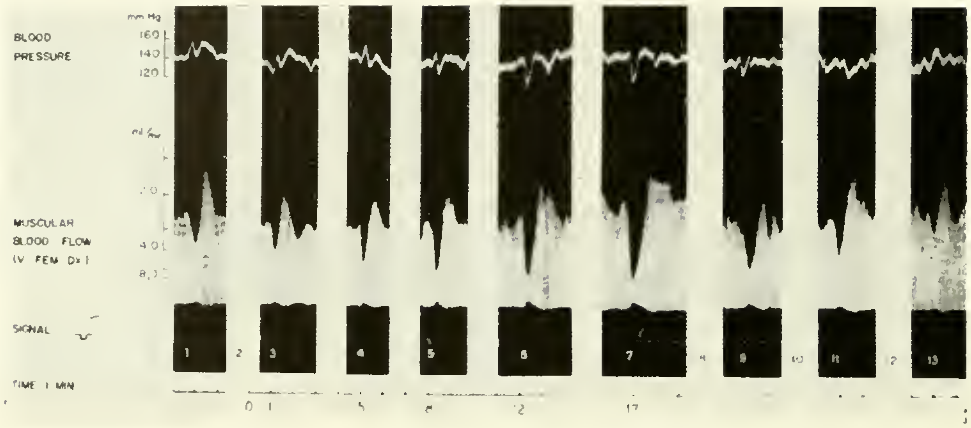

FIG. 11. Vasodilator responses in the muscles of the hind leg to stimulation in the right part of the tectum mesencephali, and the effect of physostigmine and atropine. Cat under Dial anesthesia; left common carotid occluded. *1*) Stimulation, 1.25 v.; 10 sec.; increase of flow, 50 per cent; *2*) physostigmine, 0.1 mg per kg, intravenously; *3*) stimulation, 1.25 v.; 10 sec.; increase of flow, 50 per cent; *4*) stimulation, 1.25 v.; 10 sec.; increase of flow, 70 per cent; *5*) stimulation, 1.25 v.; 10 sec.; increase of flow, 130 per cent; *6*) stimulation, 1.25 v.; 10 sec.; increase of flow, 170 per cent; *7*) stimulation, 1.25 v.; 10 sec.; increase of flow, 260 per cent; *8*) atropine, 0.2 mg per kg, intravenously; *9*) stimulation, 1.25 v.; 10 sec.; increase of flow, 110 per cent; *10*) atropine, 0.3 mg per kg, intravenously; *11*) stimulation, 1.25 v.; 10 sec.; increase of flow, 70 per cent; *12*) atropine, 0.5 mg per kg, intravenously; *13*) stimulation, 1.25 v.; 10 sec.; increase of flow, 20 per cent. Note the potentiating effect of physostigmine and the large doses of atropine necessary for abolishing the vasodilator responses. [From Lindgren (149).]

Medulla Spinalis and Medulla Oblongata

In the medulla oblongata the sympathetic vasodilator pathway was found to lie in the ventral lateral area [Lindgren & Uvnäs (151, 152)]. It forms a longitudinal band running 1 to 2 mm above the ventral surface of the medulla and could be traced down to the lateral horns of the cervical segments of the spinal medulla.

Electrical stimulation of the medullary part of the sympathetic vasodilator path produced in cats and dogs ipsilateral vasodilatation in the skeletal muscles of a hind leg (fig. 12) accompanied by ipsilateral vasoconstriction in the skin of the hind leg (cat) and in the ear (dog) and within the splanchnic region [Lindgren (149)]. In addition, stimulation produced a discharge of catechols from the adrenals [Grant *et al.* (106)]. Evidently the vasodilator fibers were accompanied by vasoconstrictor fibers and fibers running to the adrenals.

Lindgren (149) showed in chronically decerebrate cats that the vasodilator and vasoconstrictor fibers in the medulla oblongata degenerated after decerebration caudal to the inferior colliculus. This finding suggests that these fibers pass through the medulla oblongata without synapses. The vasodilator path passes outside those medullary regions which contain the pressor and depressor centers. In point of fact, Lindgren & Uvnäs (153, 154) showed that with cauterization it was possible to destroy the depressor region and thus to abolish medullary depressor reflexes produced by stimulation of a sinus nerve, depressor nerve or afferent nerve. Such local destruction of the depressor area does not interfere with the sympathetic vasodilator pathway, since Lindgren & Uvnäs demonstrated that hypothalamic stimulation still produced vasodilatation in the muscles, which finding must imply that this path passes intact through the medulla oblongata.

Mesencephalon

Lindgren (149) found that the sympathetic vasodilator pathway from the hypothalamus could be traced towards the mesencephalon. He found it to lie in the basal parts of the superior colliculus whence it continued ventrocaudad to the upper part of the medulla oblongata where it descended dorsolateral to the pyramidal tract. He further observed that the tectofugal pathway had a partial crossing ventral to the substantia grisea centralis approximately in the

FIG. 12. Concomitant vasodilator responses in muscles of right hind leg (*upper record*), and vasoconstrictor responses in skin of right ear (*lower record*) during stimulation of right half of medulla. Dog with spinal cord ligated at L5. Voltage: 1.25 v. Duration of each stimulation, 15 sec. Vasodilator responses in right leg disappear but cutaneous vasoconstrictor responses in ear persist and cause pressor response after atropine. [From Lindgren & Uvnäs (152).]

region of the decussatio dorsalis tegmenti. Stimulatory exploration revealed that supracollicular and collicular stimulation produced bilateral vasodilator responses in the skeletal muscles, while infracollicular stimulation resulted only in ipsilateral responses. The same was the case with vasoconstrictor responses in the skin. From this observation, Lindgren concluded that the mesencephalon constitutes the lowest integrating level for the vasodilator tract. Following supracollicular decerebration, vasodilator responses persisted on stimulation after a sufficient length of time had elapsed for degeneration of the severed neurons. This persistence of vasodilator responses must mean that fresh neurons originated from the collicular area.

Hypothalamus

Intrahypothalamic stimulation produces vasodilatation in the skeletal muscles of both the cat and the dog [Eliasson *et al.* (75, 76)], in the cat frequently accompanied by vasoconstriction in the skin of the paw and in the intestines. In the dog, on the other hand, it elicited a more or less selective activation of the sympathetic vasodilator outflow. Neither acceleration of the heart nor other signs of sympathetic activity were observed to occur. The vasodilatation produced in the muscles could amount to five or six times the basal value; it could be made maximal (fig. 13) and could arise without any significant changes in the arterial pressure, evidently because compensatory vasoconstriction simultaneously occurred elsewhere. Vasodilatation elicited by hypothalamic stimulation was invariably bilateral.

In the experiments of Uvnäs *et al.* sympathetic vasodilator discharges could be evoked only by stimulation within a fairly limited area of the hypothalamus extending along the mid-line. This finding contrasts with the diffuse distribution of pressor and depressor points throughout the hypothalamus, notably the lateral part, reported by earlier workers.

Since the sympathetic vasodilator outflow can also be activated by intrahypothalamic stimulation in chronic decorticate animals [Eliasson *et al.* (77)], the cell bodies of these vasodilator neurons are located in the hypothalamus where a vasodilator path originates. This path in its hypothalamic course ran from 3 mm rostral to the anterior commissure between the internal capsule and the mid-line, extending caudad along the mid-line in a somewhat dorsocaudolateral direction, reaching the ventromedial border of the ventrothalamic nuclei. During its posthypothalamic course it ascends steeply towards the tectal region where it reaches a position in the collicular area about 3 mm beneath the dorsal surface of the brain stem and 3 to 5 mm lateral to the mid-line.

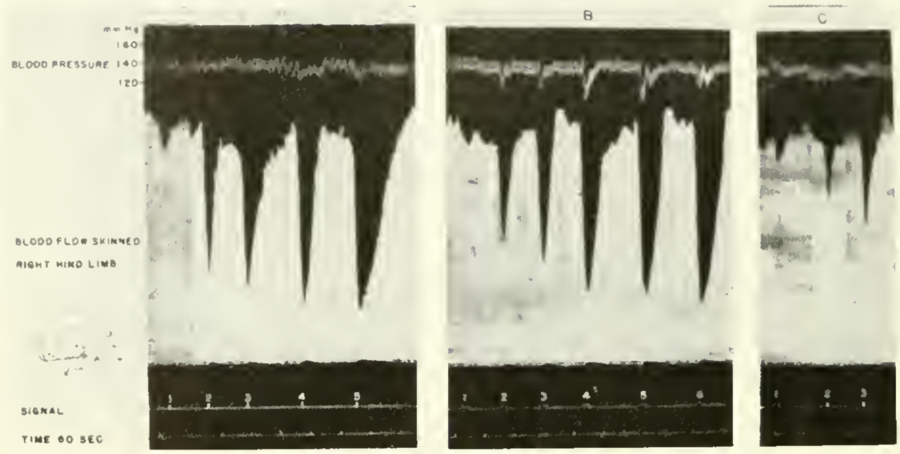

FIG. 13. Vasodilator responses in skinned hind leg of a dog. *A*: Responses after intra-arterial injection of acetylcholine; *1*) saline control, increase of flow 10 per cent; *2*) 0.002 μg, 150 per cent; *3*) 0.02 μg, 170 per cent; *4*) 0.2 μg, 270 per cent; *5*) 2 μg, 300 per cent. *B*: Responses to hypothalamic stimulation for 15 sec.: *1*) 0.5 v. intensity, increase of flow 5 per cent; *2*) 0.75 v., 80 per cent; *3*) 1.0 v., 120 per cent; *4*) 1.5 v., 190 per cent; *5*) 2.0 v., 240 per cent; *6*) 2.5 v., 280 per cent. *C*: Responses after 0.1 mg per kg atropine: *1*) stimulation with 1.5 v., increase of flow 10 per cent; *2*) 0.02 μg acetylcholine, 25 per cent. [From Eliasson *et al.* (76).]

Cerebral Cortex

Eliasson *et al.* (76) presented evidence showing that the sympathetic vasodilator outflow has a cortical representation. Vasodilator responses were observed on electrical stimulation of the motor cortex of the dog in an area between the cruciate sulcus and the sulcus considered to be homologous to the fissure of Rolando. Eliasson *et al.* also observed a few subcortical vasodilator points indicating the existence of a corticohypothalamic pathway. The available histologic data do not allow any definite conclusions regarding the anatomical course of these vasodilator neurons. However, the latter seem to pass from the cortex within the internal capsule to structures in the anterior part of the hypothalamus.

Physiologic Significance of Sympathetic Vasodilator Nerves

It is somewhat remarkable that notwithstanding our fairly wide knowledge of the cerebral representation of the sympathetic vasodilator outflow, we know virtually nothing about its functional significance. In my own opinion the contributions recently made by Swedish investigators lend considerable weight to the view that the sympathetic vasodilator outflow is limited to the skeletal muscles, at all events in the dog and cat. This at least applies to that sympathetic vasodilator outflow the intracerebral representation of which has been studied by these investigators.

The vasodilatation in skeletal muscle observed by Green & Hoff (107) and Lund (157) on stimulation of the sigmoid gyrus in cats or areas 4 and 6 in monkeys was attributed by them to diminution of vasoconstrictor tone. However, in the absence of decisive evidence, one might ascribe it equally well to activation of the vasodilator system.

The fact that the sympathetic vasodilator outflow has cortical, hypothalamic and mesencephalic relay stations suggests that it in some way takes part in the integrative control of the muscle blood flow. It is generally considered that the response pattern characterizing emotional reactions such as fear, anger, anxiety, sexual excitement and other situations requiring sudden mobilization of the organism's resources is in some way dependent on the integrative action of the hypothalamus. The increase in the cardiac output that attends muscular work is distributed, by means of shifts of tone in the peripheral vessels, chiefly to the muscles. Activation of the sympathetic vasodilator outflow by hypothalamic stimulation gives rise to a redistribution of blood that is characteristic of emergency reactions. This system can produce vasodilatation in the muscles and simultaneously vasoconstriction in the skin and viscera. Further, there is activation of the adrenals, with selective liberation of epinephrine. The amounts thus liberated do not suffice to produce vasomotor reactions in the muscles and skin, but they are sufficient to increase the metabolic processes in the muscles, heart and other organs. One is tempted to assume, therefore, that the sympathetic vasodilator nerves are activated in circumstances which require optimal conditions for muscular effort.

The question arises whether or not the sympathetic vasodilator nerves may be involved in the control of

the muscle blood flow even if the organism is not under stress. It is well known that the initiation of voluntary muscular activity is accompanied by instantaneous, or even anticipatory adjustments in the respiratory and circulatory systems to meet the increased metabolic demands, adjustments occurring with such rapidity that the effector mechanisms are necessarily nervous. Since the vasodilator neurons have their origin in the motor cortex, they may be concerned in some way with the initial adjustment of the muscle blood flow during exercise.

Although the sympathetic vasodilator nerves may play some part in the initial rise of blood flow in the muscles at the start of muscular exercise, they are not necessarily involved in the regulation of the muscle blood flow during exercise. Numerous British investigators have shown, in both animals and man, that adequate vasodilatation occurs during exercise even in the muscles of a sympathectomized extremity.

No evidence has emerged to show that the sympathetic vasodilator nerves are involved in depressor reflexes, at least in anesthetized animals. The depressor center of the medulla oblongata can be destroyed locally, and medullary vasodepressor reflexes thus abolished, without affecting the sympathetic vasodilator pathway.

The sympathetic vasodilator tract, and also those vasoconstrictor fibers that accompany it, does not appear to exert any tonic influence on skeletal muscle vessels, again in anesthetized animals, since in them section of the pathways in their medullary portion does not affect the blood flow in the skeletal muscles.

OBSOLETE VASODILATOR CENTER HYPOTHESIS

When Bayliss early this century propounded his vasodilator center theory, which he subsequently elaborated in his monograph of 1923 (29), he assumed that this center had not only an inhibitory reciprocal action on the vasoconstrictor center, but also exerted a direct influence on the tone of the peripheral vascular bed by tonic discharges via vasodilator nerves. In his view, gained from experiments on dogs and rabbits, the sympathetic vasoconstrictor tone was slight or quite inappreciable in those animals. He was therefore obliged to attribute depressor reflexes largely to excitation of vasodilator nerves rather than to inhibition of vasoconstrictor tone. Since Bayliss was unaware of the existence of sympathetic vasodilator nerves, he had to seek vasodilator nerves of nonsympathetic origin. It was reasonable for him to assume that these should be sought in the dorsal root fibers since both his own observations and those of Stricker (196) had shown that mechanical and electrical stimulation of those fibers could produce antidromic vasodilatation. Moreover, parasympathetic vasodilator fibers were known, and they were assumed to take part in the central vasodilator nerve control of the peripheral vascular bed.

With our present knowledge of the physiology of the central nervous system, it is scarcely plausible that vasodilator impulses would be directed from the medulla oblongata in an antidromic direction, via afferent fibers, to the skin and muscles. It was to these areas that the antidromic vasodilator impulses were considered to lead. All experimental experience indicates that such a reversed synapse passage is unlikely under physiologic conditions. It is also difficult to conceive of two flows of impulses in opposite directions passing through one and the same neuron without entering areas refractory to each other and hence being abolished. It is astonishing to find that this notion of the centrally controlled antidromic vasodilator outflow still persists today, in spite of its inherent implausibilities.

Bayliss' experimental evidence, as discussed in detail by Uvnäs (204) and Folkow *et al.* (89), is by no means unimpeachable. One of his chief arguments was that depressor nerve stimulation produced reflex vasodilatation in an extremity even after sympathectomy. Yet he observed that vasodilator responses were not always abolished by complete denervation of the leg. This finding should have aroused his suspicions, but rather surprisingly he stated that "these experiments were naturally rejected." Dole & Morison (65) conducted experiments on dogs and cats with a plethysmographic technique largely conforming to that of Bayliss and found that a depressor reflex was sometimes attended by an increase in the leg volume, not only after sympathectomy, but even after total denervation of the leg—i.e. even after section of the afferent innervation—and they therefore concluded that the vasodilatation could not be of nervous origin.

Frumin *et al.* (93) employed a cross-circulation technique, measuring the blood flow in the femoral artery. With depressor reactions elicited in different ways, they observed an increase of blood flow in the cross-perfused leg. This reflex increase generally disappeared after sympathectomy, but whenever it persisted it was due to the presence of an overlooked collateral circulation in the cross-perfused leg. The moment this collateral circulation was eliminated, all

postsympathectomy reflex vasodilator responses disappeared.

Nor has direct stimulation of the vasodilator region in the medulla oblongata yielded evidence of the existence of vasodilator nerves [Lindgren & Uvnäs (153, 154), Frumin *et al.* (93)]. A cross-circulation technique permitting the blood flow to be studied independently of the falls in arterial pressure revealed very substantial rises of blood flow in muscles and cutaneous vessels of the cross-perfused leg. Neither of the above-named groups of authors were able to find even the slightest increase of flow in muscles or skin after sympathectomy. Sensory denervation (section of the spinal cord below L4), on the other hand, had no influence whatsoever on the vasodilator effects that were produced by stimulation of the depressor area.

Bach (19) is one of the last advocates of the vasodilator center theory. In his opinion the dorsal root vasodilator system exerts a tonic vasodilator control. Using cats in which almost the whole spinal cord was exposed, he developed a method for rapid and complete section of all the dorsal or ventral nerve roots from the fourth cervical to the fourth lumbar nerves. In those cats in which the arterial pressure at the start of the experiment was sufficiently high (100 to 130 mg Hg) to permit a study of depressor reflexes, stimulation of a depressor nerve produced a slow, but well-defined, decrease in arterial pressure. Following resection of all the dorsal roots the pressure rose 20 to 40 mm Hg, from which Bach concluded that these nerves normally exerted a vasodilator tone. The fact that no depressor reflexes were obtained in the deafferented animal, even though the sympathetic vasoconstrictor innervation was intact, provided "direct evidence that the dorsal root fibers are an essential pathway for initiation of the reflex vasodilatation."

Against Bach's conclusion the objection can be raised that inhibition of vasoconstrictor tone has been indisputably demonstrated in depressor reflexes. Apparently in Bach's experiments the animals were in such poor condition that vasoconstrictor tone had disappeared. It may be added that cutting of the dorsal roots with the technique used by Bach was bound to evoke a violent discharge, with reflex vasoconstriction and adrenal secretion, so raising the arterial pressure.

Since antidromic vasodilator impulses were considered chiefly to pass to the skin, they might conceivably mediate cutaneous vasodilatation of central origin. Folkow and his associates (88, 89) produced marked vasodilatation in the skin of the cat paw by diathermic heating in the temperature-regulating area of the anterior part of the hypothalamus. Sympathectomy—acute or chronic—completely abolished this response; however, it remained unchanged after sensory denervation of the paw.

On the basis of the accumulated experimental evidence it is, therefore, safe to conclude that there exists no centrally controlled antidromic vasodilator outflow via dorsal root fibers. Such a statement does not, of course, mean that antidromic vasodilator nerves are nonexistent. On the contrary, antidromic vasodilator impulses certainly play an important role in the local regulation of cutaneous circulation. However, the physiology of axon reflexes is beyond the scope of this article.

As mentioned above, parasympathetic vasodilator nerves were also thought to be involved in Bayliss' vasomotor regulation mechanism. The experimental evidence for the participation of these nerves in pressor and depressor reflexes is even less impressive than for that of dorsal root fibers. Celander & Folkow (52), like Lindgren & Uvnäs (153, 154), were unable to find any evidence of an activation of parasympathetic vasodilator fibers to the tongue or the intestines in depressor reflexes elicited by stimulation of afferent vagal fibers or by direct electrical stimulation within the medullary depressor area.

The hypothesis of a bulbar vasodilator center implies the existence in the medulla oblongata of an integrating area which relays incoming impulses to various vasodilator nerves. If the hypothesis were true, it should be possible to activate the center by eliciting reflex vasodilation or by direct local stimulation of the structures in question.

Since vasodilator nerve discharges occur neither in depressor reflexes evoked by afferent stimulation of a sinus, a vagus or a peripheral sensory nerve, nor in vasodilatation produced by stimulation in the depressor area, the aforementioned requirements for the existence of a vasodilator center within the depressor area are lacking. On the whole, there seems no reason whatsoever to assume the existence of a bulbar vasodilator center in the sense that this center would form an integrative area governing the activity in the various vasodilator nerve outflows.

It is true that a discharge in the sympathetic vasodilator nerves to the skeletal muscles can be brought about by direct stimulation within a 'vasodilator band' running in the rostrocaudal direction in the ventrolateral part of the medulla oblongata. How-

ever, this 'vasodilator band' forms the bulbar part of that sympathetic vasodilator outflow to the muscles which, originating in the motor cortex, passes to the spinal cord. There are no experimental data to support the opinion that it is an integrative vasodilator area.

The tonically active vasomotor areas of the medulla, the pressor and the depressor areas, thus modulate vascular tone solely by varying the vasoconstrictor discharge, as schematically outlined in figure 14.

VASOCONSTRICTOR INHIBITION AND VASODILATOR ACTIVATION: TWO FUNCTIONALLY SEPARATE VASODILATOR MECHANISMS

The vasodilatation associated with medullary vasodepressor reflexes, as pointed out above, is due to a reduction of vasoconstrictor tone. This vasodilatation is totally abolished by sympathectomy but is quite unaffected by sensory denervation. Further, it is abolished by sympatholytic drugs which block the effect of the vasoconstrictor transmitter. Vasodilatation due to inhibition of vasoconstrictor tone is not influenced by atropine.

In skeletal muscles vasodilatation can be produced by intracerebral stimulation of sympathetic vasodilator nerves. Atropine, as has been repeatedly pointed out, completely abolishes these vasodilator effects since the sympathetic vasodilator fibers are cholinergic. The complete subsidence of vasodilatation shows that it is not due to inhibition of vasoconstrictor tone.

There are, accordingly, two vasodilator mechanisms, effected via sympathetic nerves: *a*) inhibition of vasoconstrictor tone and *b*) initiation of vasodilator activity. Available evidence suggests that these two vasodilator mechanisms are functionally separate. Destruction of the depressor region in the medulla oblongata abolishes the medullary vasodepressor reflexes [Scott (192), Lindgren & Uvnäs (153, 154)] but has not the slightest effect on the sympathetic vasodilator outflow in the medulla oblongata. Hypothalamic stimulation, for instance, is still able to produce vasodilatation in the skeletal muscles [Lindgren & Uvnäs (153, 154)]. The two vasodilator mechanisms, vasodilator activation and vasoconstrictor inhibition, have never been experimentally observed to be elicited simultaneously.

Other vasodilator nerves, the vasodilator to the

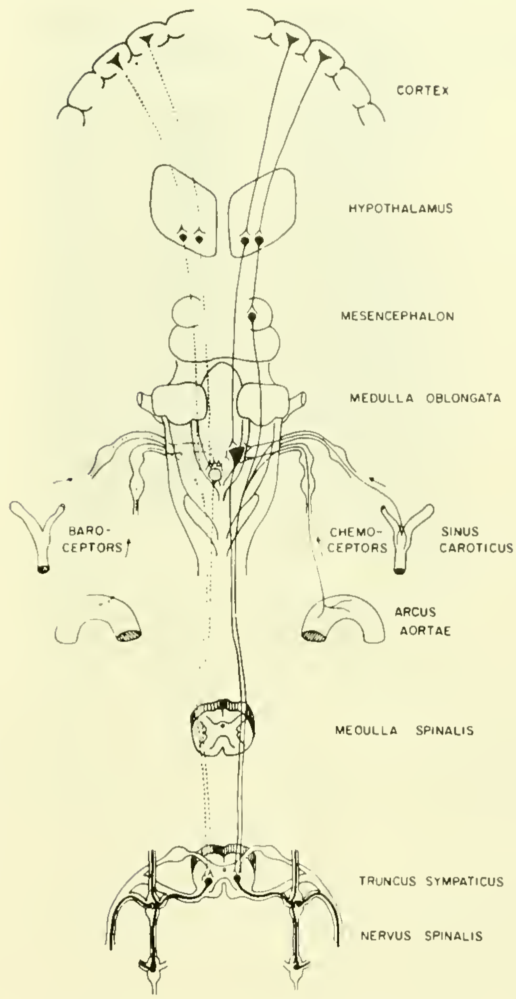

FIG. 14. Schematic drawing showing supramedullary and afferent influences on the medullary pressor and depressor areas, and the projection of excitatory and inhibitory impulses on the spinal vasomotor neurons. —— Sympathetic vasoconstrictor fibers; .... sympathetic vasodilator fibers; ▼ medullary pressor area, ⊙ medullary depressor area.

tongue and to the erectile tissues of the genitals take part in the local regulation of blood flow according to the needs of the local activity.

The vasodilator outflows seem to be devoid of tonic activity and there is no interaction between the vasoconstrictor and the vasodilator outflows. However, all experiments designed to elucidate the organization of the central vasomotor control have been performed on narcotized animals. Anesthesia, without doubt, has a strong depressive action on supramedullary synapses and neurons. The possibility is not excluded, therefore, that in the nonanesthetized animal the

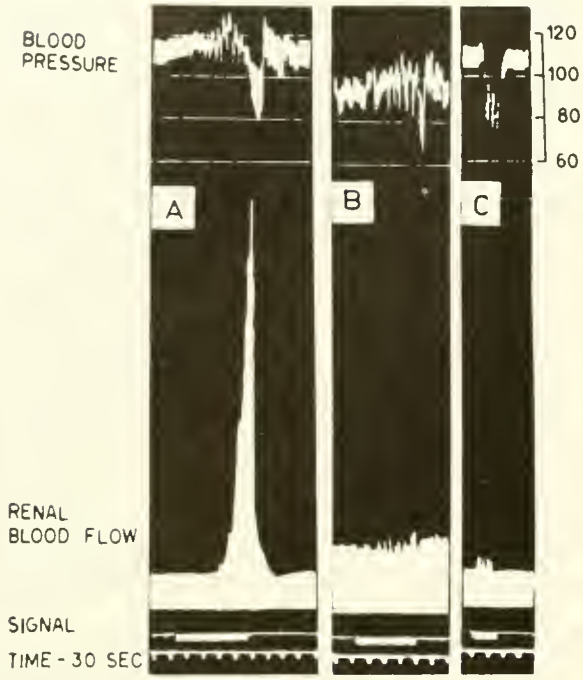

FIG. 15. Adjustments of renal blood flow during asphyxia. *A:* Asphyxia for 2 min. 15 sec. with sympathetic innervation and adrenals intact. *B:* Asphyxia for 1 min. 50 sec. with sympathetic innervation cut. *C:* 'Perfusing' arterial pressure lowered by partial occlusion of abdominal aorta. [From Celander (51).]

vasodilator nerves both have a spontaneous activity and participate in integrating mechanisms not revealed in animals under anesthesia.

NERVOUS CONTROL OF VENOUS SYSTEM

There are indications in the earlier literature that vascular reflexes influence vasomotor tone not only on the arterial but also on the venous side. Quite recently Alexander (8), using the distensibility of veins as the criterion of such responses, observed venoconstriction following evocation of pressor reflexes by central vagal stimulation, carotid sinus hypotension, hypercapnia and hypoxia. Dilatation of the venous bed occurred with carotid sinus hypertension. Alexander showed too that venomotor tone rises sharply with hemorrhage. In reversible shock venomotor tone rose commensurately with recovery. In irreversible shock, on the other hand, venodilatation occurred which Alexander (9) concluded led to pooling of blood in the venous system, an important factor in circulatory failure.

Measurements of venomotor tone in anesthetized dogs revealed a reflex mechanism capable of dilating the intestinal veins in response to an elevation of pressure in the abdominal caval system. "Acting subordinate to the buffer reflexes of the arterial side of the circulation these venous reflexes would serve to adjust venous capacity to venous load so as to contribute to homeostasis in a vascular system" [Alexander (10)].

SIGNIFICANCE OF THE ADRENAL MEDULLA IN CARDIOVASCULAR REGULATION

The commonly used term, 'the sympathicoadrenal system,' reflects the view that the sympathetic nervous system has two effector components, a direct, nervous and a hormonal, adrenal. The discharge of catechols from the adrenal medulla is thought to reinforce the direct action of the nervous impulses in the sympathetic nerves. This concept arose particularly from the work of Cannon and his associates on responses to the various emergency states. These responses have been described by Cannon (49), Cannon & Rosenblueth (50) and others.

The general subject of adrenal medullary secretion is presented in Chapter VII of this *Handbook* by von Euler. Here there will be considered recent work by Celander (51) throwing doubt on the validity of the concept that adrenal medullary secretion plays any significant role in cardiovascular regulation. Celander stimulated the splanchnic nerves of cats and determined the rate of the resulting epinephrine and norepinephrine secretion. Infusing the catechols intravenously at this rate, he found the vascular effects to be small compared with those produced by the original stimulation of the splanchnic nerve. Again, the intense vasoconstriction in the skin, the skeletal muscles and the kidneys produced by asphyxia became insignificant after sympathectomy in spite of intact adrenal innervation (fig. 15). Celander further showed that the vascular changes produced by stimulation of the sympathetic nerves to a vascular area, with optimal frequency of stimuli, were 10 to 20 times greater than those elicited by the adrenal catechols secreted as the result of corresponding stimulation of a splanchnic nerve.

The observations of Celander are important since they strongly suggest that the central vasomotor control is dominated by the neural component. It may be questioned whether the adrenals under physiologic conditions play any significant role in the central vasomotor control.

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Central control of digestive function

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CHAPTER CONTENTS

ROLE OF THE CENTRAL NERVOUS SYSTEM IN DIGESTIVE FUNCTION

THE MAIN FUNCTIONS of the digestive system are mechanical and chemical subdivision of the ingested material, transportation, absorption and excretion. These functions present no problem in the one-celled animal but become increasingly complex at the higher developmental stages. The increase in size of the animal and the introduction of regions with specialized functions in the digestive system parallels the development of local nervous mechanisms with regulatory functions. These consist of groups of nerve cells which coordinate activity in neighboring regions of the alimentary canal. These cells presumably also receive impulses from receptors in the wall of the intestine. When a central nervous system is developed, some of the information about the state of the digestive system is transmitted to the brain. In the brain the information is correlated with information received from other sources which have direct or indirect influence on the digestive functions. The integrated response is relayed to the local regulatory mechanism or directly to the effector organs. Thus the central nervous system exerts partial control over the activity in the digestive system.

The pertinent questions regarding the relationship between the central nervous system and the digestive system are, first, to what extent does the central nervous system participate in normal digestive function? And second, to what extent do pathological changes in one system affect the other? An attempt to provide an answer to these questions must take into consideration the fact that different animals may have found different solutions to the same problems. The primary requirement that nutritional substances of the right consistency and in the correct amount are distributed over a surface suitable for absorption must be met. (The control of food intake by hunger and appetite is considered in Chapter XLVII of this *Handbook* by Brobeck.) In animals with similar anatomical structure and nearly identical requirements, the relative importance of central and peripheral factors may still vary.

It is theoretically possible to reach an answer to the simple question of the importance of the central nervous system for digestion (or for any other function) simply by removing as much of it as possible. Such an experiment can definitely give us information as to whether the organism can or cannot perform digestive functions after the procedure. It does not give any information about the normal participation of the central nervous system in digestive function. Removal of small localized regions of the brain or cord may cause a change in the output to the digestive system whether the removed region was a part of the central control system for digestive function or not.

Electrical stimulation of various regions of the brain will cause changes in the activity of the gastrointestinal canal. These regions then have access to path-

ways for impulses to the digestive system. Not all of these areas probably are normally concerned with regulation of digestive function. The areas found must fill one of two qualifications. They must be concerned with the initiation or performance of one particular function, in which case this function must be permanently damaged by removal of the area; or they must be concerned with the modification of digestive function according to information of importance to the system. In the first case electrical stimulation will initiate what is usually a spontaneous event; in the latter, it will imitate the arrival of impulses which lead to a modification of digestive function. In the latter case the incoming impulses can be from the digestive system or from some other system. If we then establish a series of areas which on stimulation change digestive function, we must also establish the nature of impulses incoming to those areas.

It is conceivable that we might acquire some idea about the basic relations between the central nervous system and the digestive system by a study of the phylogenetic development of the relations between the two systems. The information available is rather scanty, however, as will be seen in the following pages.

COMPARATIVE PHYSIOLOGY

The coelenterates have a diffuse network of nerve fibers with intermingled cells. Part of this network is located in the gastrodermis. It is not clear whether the nerve net participates in the extracellular digestion or not, but it is probably connected with the feeding mechanisms (82). These mechanisms reach a high degree of complexity at a stage when transport of the ingested food is still effected through simple flow ciliary motion or the accessory action of the body wall. Only exceptionally does the nervous system participate in the regulation of ciliary action (64). Rhythmic movements of the gastrointestinal canal appear first in the gastropods and rhythmic secretion after feeding is observed in *Helix* (54). Carriker (19) found an abundance of nervous tissue about the stomach region of the snail, *Lymnaea stagnalis appressa*, indicating possible nervous control. Removal of the verticalis complex in the brain of the cephalopods inhibits food intake for several days according to Sanders & Young (79) but does not affect the digestive process. In annelids the influence of the nervous system on the gastrointestinal tract is remarkably similar to the relations in primates. Excitatory and inhibitory fibers can be demonstrated (66), and Wu (97) found that electrical stimulation of the annelid brain inhibited or excited gastrointestinal motility.

The arthropoda show a great variety in structure of the feeding tube depending on the type of food ingested, but little evidence has been brought forward indicating nervous control. The insects have innervation to the anterior portion of the gut from the forebrain, possibly via the subesophageal ganglion. Gersch (38) showed that stimulation of the nervous system in the gnat *Corethra* caused antiperistaltic movements. The functions of the visceral nervous system in lower animals remain obscure.

Even if the stomach appears first as a specialized structure in the fishes, there is no evidence that these animals need the central nervous system for gastrointestinal coordination. The goldfish can perform its gastrointestinal functions without a brain (82). Amphibians and birds lose their feeding reactions after removal of the brain, but whether this is due to lack of initiative or involves coordinating mechanisms is not clear. Decerebrate mammals show definitely a lack of initiative, but food placed in the pharynx will be swallowed and adequately digested.

Even if we have ample morphological evidence that the central nervous system and local nervous networks enter into relation with the gastrointestinal system at a fairly early stage in development, there is little proof of a constant physiological relationship. For comprehensive reviews of the role of the peripheral nervous system see Yonge (98) and Colin Nicol (21).

MASTICATION

Rhythmic chewing can easily be elicited by electrical stimulation of the lower part of the motor cortex. Repeated observations in a wide variety of animals have confirmed this observation (31, 65, 78). Experiments by Bechterew (15) seemed to indicate the presence of a subcortical center, located in the substantia nigra and responsible for the rhythmicity in chewing. Magoun *et al.* (60) established that rhythmic chewing could no longer be obtained on stimulation of subcortical regions after cortical extirpation. Bremer (17) had earlier denied, on theoretical grounds, the existence of a subcortical station. It was not possible for Rioch to confirm Bremer's observation that the cortical masticatory center was divided into three parts. Instead he postulated that the main function of the cortical masticatory center was to inhibit the tone of the jaw openers, and that

proprioceptive reflexes would then cause the rhythmicity in the movement. That it is possible to produce rhythmical chewing on stimulation of subcortical areas was shown by Hess & Magnus (47). The regions stimulated by these authors were localized in the ventral nucleus of the thalamus, in the hypothalamus and in the septal areas.

In addition to these observations which may pertain to different parts of the same pathway, Rioch & Brenner (77) showed that irregular licking, chewing and swallowing could be elicited by electrical stimulation of the region of the tuberculum olfactorium and the lobus pyriformis. Similar observations had been made earlier by Schaltenbrand & Cobb (81). Gastaut *et al.* (37), Vigouroux *et al.* (91) and Kaada (50) found that the effect was mainly due to activation of the amygdaloid nuclei or efferent fibers from this region. Kaada *et al.* (51) localized the responsive region to the anteromedial group of the amygdaloid nuclei.

In almost all of the observations pertaining to this second system, it has been noted that there is a long latent period before the onset of the chewing response (36). This is of considerable interest when we compare the results of similar stimulation in man. It was observed by Jackson (89) that there is a type of epilepsy characterized by masticatory seizures. These seizures have their focus in the region of the temporal lobe as described by Penfield & Jasper (72) and by Magnus *et al.* (59). Mastication is not a part of the initial seizure but belongs rather to the accompanying automatisms and does not occur when the patient is conscious. The most likely region involved would be the amygdaloid nuclei and these have connections with the septal areas, the hypothalamus and the midbrain (61). The masticatory aspect of the seizure may then be due to secondary activation of more deeply situated regions, possibly the same as those Hess & Magnus (47) and Magnus (58) have found to respond to electrical stimulation in the septal and hypothalamic areas. It is interesting to note that it has not been possible in man, in spite of frequent attempts, to reproduce the constant activation of rhythmic chewing that occurs in animals. Removal of the cortical areas implicated either in man or experimental animals does not normally seem to interfere with masticatory mechanisms. Schaltenbrand & Cobb (81) observed no deviation from the normal feeding pattern after bilateral hemispherectomy in cats. If, on the other hand, the animals are decerebrated, mastication is severely impaired (13). Food placed in the mouth of the animal will stay there indefinitely. Destruction of the temporal areas does not affect digestive function in animals (73).

It must then be considered highly questionable if the amygdaloid areas normally have anything at all to do with the chewing mechanisms. The role of the motor cortex is doubtful in man. As first suggested by Magnus *et al.* (59), mastication, like walking, may be one of those automatic functions which in man have become localized in subcortical regions.

SWALLOWING

The act of swallowing is a mechanically complicated act which in the higher mammals involves some 20 muscles which act together in groups. The process does not depend on activation of these muscles in a certain order, as shown by the fact that destruction of one muscle does not affect the act of swallowing appreciably (25). Nor is there then reason to believe that proprioceptive fibers from one muscle facilitate the activation of the next muscle in the pattern. Meltzer (63) postulated in 1899 that the orderly progress of deglutition must be of central origin. He thought that afferent impulses arriving at the center of deglutition traveled through this in orderly fashion, activating cell groups innervating the pharyngeal muscles and the esophagus. It had been established by Pommerenke (74) that swallowing was impossible without an afferent stimulus and Meltzer added the observation that, once initiated, the swallowing act did not require further afferent stimulation. In order to explain the central mechanism of the swallowing act we would have to assume that the afferent stimuli set up an excitatory process in the motor nuclei, either through specific pathways or through a diffuse interneuronal system (25). The small changes that occur from swallow to swallow which were observed by Doty & Bosma with electromyography make it unlikely that specific pathways could exist. We would still have to assume that there is some regulating factor which governs the delay in the interneuronal system so that the impulses arrive at the appropriate motor nuclei in orderly fashion.

The nature of this regulating factor remains unknown. Stimulation of the posterior part of the pharynx does not evoke only swallowing responses. Retching, gagging and salivation can also occur and it is conceivable that psychic factors or sensory stimulation from taste and smell receptors may be necessary to determine the type of response to afferent stimulation. We have some experimental evidence

that supranuclear regions influence the swallowing response or can in themselves initiate a swallowing movement. Part of the response to amygdaloid stimulation is a swallowing movement (50), and Hess & Magnus (47) have observed swallowing in response to hypothalamic and septal stimulation. None of these regions are necessary for the performance of swallowing movements since the decerebrate animal swallows if food is placed far back in the pharynx (13). Nor can any of these regions or any other region inhibit a swallowing movement once started. Following the initiation of the movement, activation of medullary and spinal nuclei follow and the activity is independent of the status of the esophagus. The excitation may spread to the stomach since Lorber *et al.* (57) showed that sham feeding changed gastric motility. Superior laryngeal nerve stimulation changes the motility of the small intestine (5). That there may be some local regulation is indicated by the fact that the spinal animal shows reflex opening of the cardia if the lower part of the esophagus is distended.

GASTROINTESTINAL MOTILITY

The empty stomach has a certain degree of tonus and a basic rhythm. When food enters the stomach or when a distended balloon is introduced, a receptive relaxation occurs which is later followed by an increase in tone and an augmentation in frequency and amplitude of the peristaltic waves. Sensory stimulation, certain psychic phenomena and nausea are accompanied by changes in tone and motility of the gastrointestinal tract. It is apparent that both central and peripheral factors participate in the control of gastric motility. Many attempts have been made in a wide variety of animals to study the absolute and relative role of these factors (6).

The studies of the peripheral factors with which we are concerned are those which refer to the central projections of the distention receptors in the stomach. Other peripheral impulses arising in the stomach or the peritoneal cavity have been of interest. Without especially studying the gastric fibers involved, Bailey & Bremer (11) in 1938 established the existence of vagal projections to the orbital surface. These observations have been repeatedly confirmed, and Dell & Olson (24) showed that there are also vagal projections to the amygdaloid region. Splanchnic projections and pathways have been studied carefully (1, 3, 35). The projection areas for these fibers were found in the somatosensory cortex (2, 26, 27). Along their pathway splanchnic fibers make connections with the reticular formation, and impulses in these fibers affect the central excitatory state of the brain (34, 86, 87).

It was later shown by Paintal (67) and Iggo (48) that there are tension receptors in the stomach and that these send impulses via the vagus nerves. The central projections of these end organs have not yet been found. Eliasson (29) found that varying the distention of the stomach changed the effect of cortical stimulation on gastric motility although only quantitatively. Similar variations in response occurred on stimulation of the vagus nerves (68). It is likely that the impulses aroused by distention could influence the net effect of cortical or hypothalamic stimulation via the midbrain. The changes in gastric motility noted by Eliasson (30) following stimulation of extensive areas in the midbrain may be regarded as unspecific effects of reticular formation activation or as effects of stimulation of afferent fibers belonging to different systems (23). Babkin & Bornstein (7) found that vestibular stimulation may cause a rhythmic type of gastric contraction which probably reflects a rhythmic discharge in the reticular formation. Much experimental work has been done on the effect of cortical stimulation on gastric motility (29, 50, 84, 88). Many fewer observations have been made on its effect on intestinal motility (88). The extensive cortical representation found in experimental animals does not seem to have any counterpart in man. Penfield's group has, in spite of many thousands of cortical stimulations, found only the area around the insula and the bands of the Sylvian fissure to be connected with gastrointestinal activity (72). Epileptic seizures involving a gastric aura were found to have their origin in this region, and electrical stimulation of the area led to vague gastric sensation and marked changes in the electrogastrogram (71). The change could be either an increase or a decrease; and, in the only case in which the insula was removed and the gastrointestinal motility observed, hypermotility was noted.

The corresponding region in animals, namely the insulo-orbital or orbital region, has been studied extensively (10, 12, 46). Vagal afferents project to this region; stimulation leads to inhibition of gastric motility or sometimes to excitation. However, ablation of the orbital surface seems to be without effect on gastrointestinal motility (9). Hess & Akert (45) obtained evidence for projection of fibers concerned with oral sense to the orbital surface. They assumed then that the orbital surface would be concerned with oral defense mechanisms. The changes in gastroin-

testinal motility might indicate that sensory fibers from the stomach also project to this area.

Another group of cortical structures which seems to be connected with gastrointestinal motor coordination consists of the subgenual portion of the cingulate, the olfactory fibers and the amygdaloid nuclei. Changes in gastric motility on stimulation of one or more of these areas have been observed by several authors (4, 8, 10, 29, 50, 51, 83, 85, 88). These areas may all be part of the same system, and the variation in stimulation effects may be due to variations in the tone of the gastrointestinal tract or to interaction at the brain-stem level. It is also possible to affect gastric movements from the sensorimotor cortex, an influence which may be exerted via the reticular formation. It must be remembered that all of the areas implicated, with the exception of a parietal region described by Eliasson (29), are parts of the cortical areas shown by French *et al.* (33) to project to the brain stem. The stimulatory effect would then not indicate that these cortical regions are specifically concerned with gastrointestinal regulation. The lack of known projections to the cortical regions discussed (with the exception of the orbital surface) would speak against their specificity. The cingulate cortex is the only part the removal of which seems to lead to increased gastric motility (9).

The hypothalamus was early implicated in the control of gastrointestinal activity. The earlier literature and the evidence for and against the existence of sympathetic and parasympathetic centers in the anterior and posterior parts of the hypothalamus were reviewed by Sheehan in 1939. Ström & Uvnäs (88) and Eliasson (30) found it possible to change the gastrointestinal response to hypothalamic stimulation by moving the electrode as little as 1 mm and could not confirm the division into sympathetic and parasympathetic regions. Probably both afferent and efferent pathways from and to the gastrointestinal tract pass via the hypothalamus, and the richness of responses to electrical stimulation may be due to the large numbers of fibers and cells in one small region. Some of the fibers must synapse since removal of the cortex does not influence the response to electrical stimulation of the hypothalamus. The changes in intestinal motility that occur on electrical stimulation indicate that adjacent segments of the alimentary canal change their motility in the same direction (88). This is not compatible with a normal regulatory function, and it is likely that the intestinal canal under physiological circumstances is relatively independent of central nervous system impulses.

VOMITING

Vomiting can be considered as an extremely complicated reflex act in which, in response to afferent stimulation, a coordinated reflex involving striated muscles, gastric musculature, respiratory movements and vasomotor reflexes takes place. If a center is to be accepted, this must be localized in the place where immediate connection with all of these different motor neurons are available. This system is not as complicated in lower animals as in man. In the lower animal the expulsion of the food contents of the stomach is mainly effected through rapid contraction of the gastric musculature with concomitant opening of the cardia or related structures (42). Most of the experimental work in this field has been done on cats and dogs. The earlier investigators thought that there might possibly be two centers, one being responsive to morphine, the other to copper salts. This was disproved by Thumas (90) who localized a vomiting center in the dog with definite anatomical limits. He found a small area in the posterior part of the rhomboid fossa which was more sensitive to the emetic action of apomorphine than any other and which on destruction made the dog insensitive to the action of apomorphine. Hatcher & Weisz (43) in repeating Thumas' experiments were led to believe that the true vomiting center was localized in the dorsal nucleus of the vagus nerve. The area localized by Thumas would then be only on the pathway for the impulses which induce vomiting.

From the large number of reflex impulses reaching the dorsal vagus nucleus one would expect vomiting and retching to occur frequently. This apparent conflict was avoided by the postulate that impulses must arrive to the center at the same time from more than one source.

Koppanyi (53) working with Hatcher demonstrated that destruction of the vagal nuclei did not interfere with the occurrence of vomiting. Only during the first days after the operation, when edema was probably still present, was there an increased threshold to apomorphine. Attempts to elicit vomiting by electrical stimulation of medullary structures failed consistently for several years. The reason for this seems to have been the difficulty to elicit vomiting in anesthetized animals. More recently, Borison & Wang (16) were able to elicit vomiting in the decerebrated animal in about 50 per cent of cases. They localized a region in the dorsal lateral part of the reticular formation of the medulla the stimulation of which resulted in projectile vomiting. Maximal inspiration occurred simultaneously. No prodromal signs, such

as salivation, nose licking or swallowing, were observed in these experiments. Bilateral vagotomy did not abolish the response. Wang & Borison (93) reported in 1950 a series of experiments on dogs in which the region responsive to stimulation was destroyed; following this the animals showed a pronounced refractoriness to chemically-induced vomiting. There was still a definite response to intragastric administration of large doses of copper sulfate which, however, might have been due to a generalized toxic action. It is conceivable that if a sufficient dose of an emetic agent is given, the direct action of the drug on the various substations of the reflex may be sufficient to induce vomiting. In spite of frequent stimulation of other regions of cat and dog brains, no report has been published in which true vomiting has been reported to occur on electrical stimulation or ablation of any other structure of the brain. Vomiting has not been seen by Penfield's group in their extensive exploration of the cortical surface of man (72). It does appear that irrespective of the afferent impulse leading to vomiting the complex process has to be integrated through a medullary structure, presumably the one described by Wang & Borison (93).

GASTRIC SECRETION

Psychic secretion of gastric juice depends on the integrity of the cerebral cortex, as pointed out by Pavlov (70). He received support in this assumption through the experiments of Guerver (41) who showed that stimulation of an area just outside the forward end of the sigmoid gyrus in dogs produced a copious flow of gastric secretion. This secretion consisted initially of a highly mucoid juice followed by hydrochloric acid and pepsin. The secretion was dependent on the integrity of the vagus nerves. Greker (40) ablated this area and found that a marked diminution in gastric secretion occurred over a period of 7 to 8 days after which the secretory values returned to normal. Many years later Watts & Fulton (94) observed, in studying the relationship of the cerebral cortex to gastrointestinal motility, that some of the stimulated animals at necropsy showed a considerable amount of secretion in the stomach. They drew the conclusion that the stimuli affecting the gastrointestinal motility also affected gastric secretion. Their observations were repeated by Davey *et al.* (22) who explored the possibility of eliciting gastric secretion by stimulating the frontal lobe in dogs and monkeys. The experimental difficulties in the collection of gastric juice are considerable because we must assume that the operative procedures including the insertion of a cannula must necessarily influence the local state of the gastric glands. It has also been clearly shown that some of the anesthetics used in themselves influence the amount of secretion even when given in very small amounts (80). Davey and his associates (22) found an area in the frontal lobe of the dog and monkey which was roughly the same as the one earlier found by Guerver and in which stimuli of long duration and fairly high frequencies activated the gastric glands. The hydrochloric acid secretion turned out to be dependent on the state of anesthesia, but pepsin and mucus secretions could be increased two to four times by stimulation of this area Injury to the area resulted in diminished response. In a discussion following the presentation of this work Davey indicated that a possible pathway would be via the lenticular nucleus, portions of the thalamus and the quadrigeminal bodies. This was on the basis of earlier reported experiments and no attempts were made to confirm this idea.

In order to facilitate the recording of the gastric acidity changes, Klopper (52) developed a method for continuous registration of gastric pH through electrodes introduced through the esophagus. These experiments showed that, on stimulation of an area just inferior to the anterior sigmoid gyrus in the cat with an optimal frequency of 15 impulses per sec. and a duration of 10 to 15 msec., a definite decrease in gastric pH was obtained. The area defined was the same as that found by Eliasson in 1952 for gastric motor function. Klopper also found that electrical stimulation of this area inhibited gastric motility which might be one reason that the duodenal secretion did not influence the gastric pH. No other portion of the cerebral cortex was found to influence gastric secretion on stimulation. The secretion of gastric juice continued up to 20 min. after the end of the stimulation This indicated to Klopper that possibly the effect of the cortical stimulation could be a release of a hormone, such as gastrin, or of histamine leading to a secondary secretion from the gastric mucosa.

Subcortical areas have long been known to react to stimulation by increasing the gastric acidity. Heslop (44) and Sheehan (84) demonstrated in connection with a study of gastric movements a definite increase in gastric acidity. Jogi *et al.* (49) observed that the secretory response to insulin-induced hypoglycemia disappears after decerebration but remains unchanged after decortication. Porter *et al.* (75)

made an extensive study of the mechanisms by which hypothalamic stimulation increased acidity and found that this could occur not only via the vagal nerves but also via the pituitary and the adrenal glands (32). A remarkable fact is the considerable latency of the change in acidity (1 to 2 hours). According to the authors the results were reliable and could be repeated. Shealy & Peele (83) found that stimulation of the amygdaloid in unanesthetized animals causes a definite increase in gastric acid content which compared favorably with that after histamine alone. They did not study the concomitant changes in mucus and pepsin secretions. These authors assumed that the effect of stimulating the amygdaloid nuclei could be mediated via histamine or via parasympathetic fibers in the vagus nerve. The pathways involved between the amygdaloid nuclei and the vagus nuclei remain unknown; it is possible that the connections between the amygdaloid nuclei and the hypothalamus may lead to activation of the hypothalamic area already earlier indicated. All types of changes in gastric secretions were obtained by Anand & Dua (4) on stimulation of temporal lobe structures with indwelling electrodes in unanesthetized cats. These authors consider the possibility that this effect is transmitted through the hypothalamus.

It seems unlikely that in the normal organism an increase in gastric secretion would occur without concomitant changes in gastric motility and vasomotor tone. If the changes in gastric secretion are mediated via a hormonal mechanism, the immediate changes in gastric motility in response to emotions, vestibular stimuli or olfactory stimuli may not be long lasting enough to elicit a change in gastric secretion also. If this is the case, central control of gastric secretions occurs only in processes associated with digestion of food.

EMOTIONAL INFLUENCE ON DIGESTIVE FUNCTION

Any emotional process can be said to consist of a subjective experience, a type of neurophysiological reaction and a mode of behavior (20). The neurophysiological reaction may affect one or many systems. The effect of emotions on the gastrointestinal tract varies, and it has been difficult to correlate a specific type of gastrointestinal change with any particular emotional change. Superficial emotional reactions may sometimes cover basic disturbances which are responsible for digestive function disturbances (62).

Emotional stress affects all parts of the gastrointestinal tract (28). Salivary secretion can be increased (69, 92) or decreased (95). Also, the composition of the saliva changes (95). Secretion of gastric juice is easily influenced by anger, joy, anxiety states, etc. (14, 96). The change in secretion is associated with or preceded by changes in motility (18). Secretion of intestinal juices and bile has been reported to fluctuate under emotional stress (69, 76, 95). Anger and hostility lead to hyperactivity of the colon; fear, to immobilization (39). Many of the older reports deal with the correlation between superficial emotions and gastrointestinal changes and do not take into consideration deeper emotional conflicts. If a change takes place in the electrical activity of the brain as a result of emotion, the change, if cortical or subcortical, will be reflected in other parts of the brain — mainly the reticular formation but also the areas to which the reticular formation projects (56). The changes may be of excitatory or inhibitory nature and can presumably also be excitatory in one part and inhibitory in another part of the brain (55). The net effect will be hard to predict and the number of possible combinations is unlimited. Under normal conditions the emotional influence will not be of major importance. One does not, however, have to postulate abnormal pathways for the influence of emotions on the digestive functions. Most of the structures that have been implicated in the neurophysiological basis of emotions have adequate connections with the lower brain-stem structures concerned with digestive function. If and when we learn to translate psychiatric terms into neurophysiological language, it will be easier to interpret the effects of emotions on gastrointestinal function.

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Central nervous regulation of body temperature

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CHAPTER CONTENTS

CENTRAL NERVOUS temperature regulation has been the subject of intensive physiologic investigation, with many sided experimental approaches, for more than seventy years. Several extensive monographs or reviews (9, 11, 19, 27, 36, 57, 59, 67, 103, 107, 110, 151, 167, 172, 174, 193, 210) have been published which have direct or indirect bearing on this subject. The present description will rely for many details as well as main conceptions on these monographs. Emphasis will be laid on function rather than structure or localization of the central nervous thermoregulatory mechanisms. Controversial evidence will be discussed mainly when such discussion seems important for general evaluation of results, or when it exemplifies important methodological problems. The text is illustrated by figures chosen from various original reports. A close study of experimental technique and evaluation of results in such figures is believed to be a valuable complement to the written description.

GENERAL CONSIDERATIONS

The homeothermic or warm-blooded animal keeps its body temperature within a few degrees C, a mean level usually around 37° to 38°C. Homeothermia is accomplished to some extent by local responses of thermoregulatory effector systems to local temperature changes, and to a greater extent by systemic responses. The systemic regulation involves: *a)* information about the body temperature, signalled to the central nervous system for receptive mechanisms situated partly in the surface layers and partly in the central layers of the body; *b)* nervous integration of such afferent signals, displayed at different levels of the central nervous system; and *c)* reactions of different effector systems, set into action by efferent nervous or humoral signals, which serve to counteract the initial change of surface or deep temperature (homeostatic effector response).

The skin and mucous membranes contain temperature receptors (103, 104), the majority of which are cold receptors, each having a characteristic temperature below 37°C for maximum activity. The minority show a maximum activity above 37°C and are there-

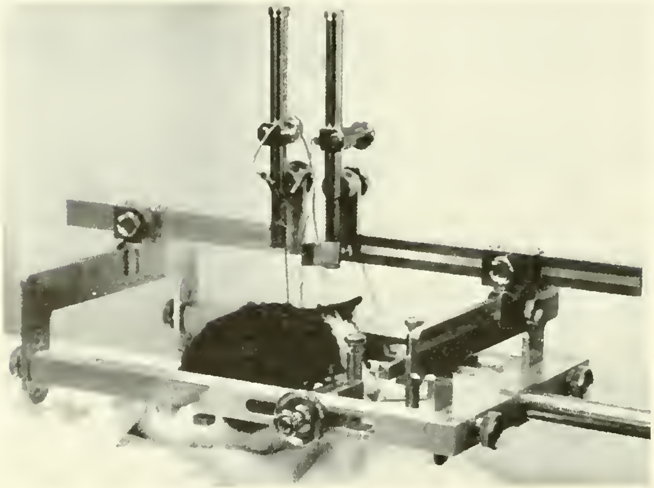

FIG. 1. *Left:* Stereotaxic instrument, modified Horsley-Clarke type, with a cat head fastened in a horizontal plane through the external auditory canals and lower orbital bone margins. One bipolar and one unipolar needle electrode are inserted into the brain from above in a known direction to a known depth. (From B. Uvnäs.) *Right:* Sagittal section of a goat skull, showing three pairs of electrode tips located in the region where the hypothalamus would be situated in the intact animal, slightly above the optic chiasma (*Ch. opt.*) and hypophysis (*Hyp.*), illustrating Hess' technique for chronic implantation of electrodes. The electrode holder is fastened by screws to the skull; electrodes are inserted through drilled holes. (From B. Andersson.)

fore warm receptors. The difference in function between cold and warm receptors is thus only quantitative. They are discussed at length by Zotterman in Chapter XVIII.

The anterior hypothalamus contains a temperature receptive region, but the structure of the sensitive elements is not known. For this reason it is preferable to refer to them as 'thermodetectors' rather than as 'thermoreceptors.'

Nervous integration of the signals from surface thermoreceptors seems to occur at all levels of the central nervous system. The integrative structures are probably, and their nervous effector systems certainly, involved in other homeostatic and coordinating mechanisms, such as the regulation of arterial pressure, water balance and skeletal muscular activity. Different functions which are served through common integrative structures will condition each other, either inhibiting or facilitating; a certain temperature receptive input may therefore result in a variable effector output (71). The effector systems and reactions available for this purpose include pulmonary ventilation, cutaneous blood flow, sweating, salivation (20), piloerection, skeletal muscular activity (21), water movements and change of body position.

EXPERIMENTAL METHODS

Information on central nervous regulation of body temperature can be gained by different experimental approaches. Some of these will be evaluated critically here.

Stereotaxic Techniques for Acute and Chronic Experiments

The stereotaxic instrument, originally devised by Horsley & Clarke (113) and later modified (166), allows the exactly guided (116) introduction of needle electrodes from above through the brain into its deeper portions, e.g. the hypothalamus (illustrated by fig. 1). The electrode tip can usually be directed to within 1 or 2 mm of a calculated position in the hypothalamus. By this technique circumscribed nervous structures can be stimulated electrically, thermally or by injection. Their electrical activity may also be recorded, or they can be destroyed by electrocoagulation to study in chronic experiments the resulting impairment of temperature regulation.

The result of local stimulation is largely judged by the responses of the thermoregulatory effector systems as an index; this is a limitation. An effector response

to such procedures as local thermal stimulation in the brain demonstrates and localizes structures with specific thermal sensitivity ('central thermodetectors') but does not give information about the unitary responses of the detectors. An effector response to local electrical stimulation in the brain may theoretically be elicited by excitation of either afferent, integrative or efferent neurons in the thermoregulatory system.

In the study of chronic brain lesions, careful histological control of the position of the lesions at necropsy is all-important and the possibility of bleeding, infection or interference with blood supply extending the destruction to other parts of the brain must also be kept in mind. In chronic experiments it is usually more difficult to measure exactly the index of response than in acute experiments; well-standardized tests have to be used (98). The general condition of the chronic animal with marked inanition (51) or infection may also severely influence the reactivity of the effector index studied; intactness of some aspect of temperature regulation may therefore be more significant than its impairment in chronic destruction experiments. The chronic studies give information about coordinated temperature regulation in the unanesthetized animal which is indispensable and cannot be gained from acute studies.

Chronic Implantation Techniques

A method of implantation of multiple needle electrodes into the brain for acute and chronic experiments has been worked out by Hess (106), as exemplified in figure 1. It is thus possible to study the effect of electrical or thermal stimulation, or of electrocoagulation, in long-term experiments on unanesthetized animals. Other types of electrodes or thermodes may be placed chronically near to the brain surface by ordinary neurosurgical procedures.

Indirect Thermal Stimulation of Brain

The brain may be warmed or cooled via its blood circulation, or by changing the temperature either of the whole body or preferably of the carotid arterial blood stream. Such a temperature change affects vascular receptive structures (29, 196, 198), and surface thermoceptors, in the whole body or only in the head, as well as large parts of the brain. The portion of the brain which is supplied by the carotid arteries varies in extent in different animals.

Temperature Measurements

It is an important and well-known fact that both the absolute level and temporal changes of temperature may show large regional variations in the body (19). This is likely to be especially true in the anesthetized animal subjected to extensive operative measures unless special precautions are taken.

The rectal temperature alone may be an insufficient measure of central body temperature (146) or of brain temperature. Like all local temperatures it is influenced by local rates of metabolism and blood flow as well as by level of central body temperature (89, 90). The oral temperature is usually a better index of brain temperature than is the rectal one. The brain temperature may, however, be measured directly both in acute (35a, 187, 203) and chronic (71, 132a, 135, 180) experiments.

HYPOTHALAMIC THERMOCEPTIVE STRUCTURES

Existence and Localization

The existence of thermoreceptive structures in the brain was suggested by Kahn in 1904 (122): warming of the carotid blood evokes signs of cutaneous vasodilatation, sweating and polypnea in the rabbit, cat and dog. Such structures were shown in 1912 to be localized deep in the brain near the corpus striatum by Barbour (8) since circulation of water at 42°C through a thermode, the tip of which was placed near the receptive structure in the rabbit brain, was found to produce vasodilatation in the ears, while cooling to 33°C produced vasoconstriction. The effect of local brain warming was repeatedly confirmed (94, 97, 148, 163, 164), but the exact localization of the responsive region long remained unknown.

A few earlier and many later reports had indicated the hypothalamus to be essential for an intact temperature regulation, or even necessary for any temperature regulation at all. It was definitely shown in 1938 by Magoun and co-workers (141) in the cat, and later confirmed in the monkey (26), that thermoceptive structures exist in the brain and that they are localized exclusively to the supraoptic and preoptic parts of the hypothalamus. In these experiments localized diathermic warming producing a moderate temperature increase of the anterior hypothalamus, but of no other regions in the brain, evoked a typical heat loss response with polypnea or panting and also sweating in the anesthetized cat (figs. 2, 3).

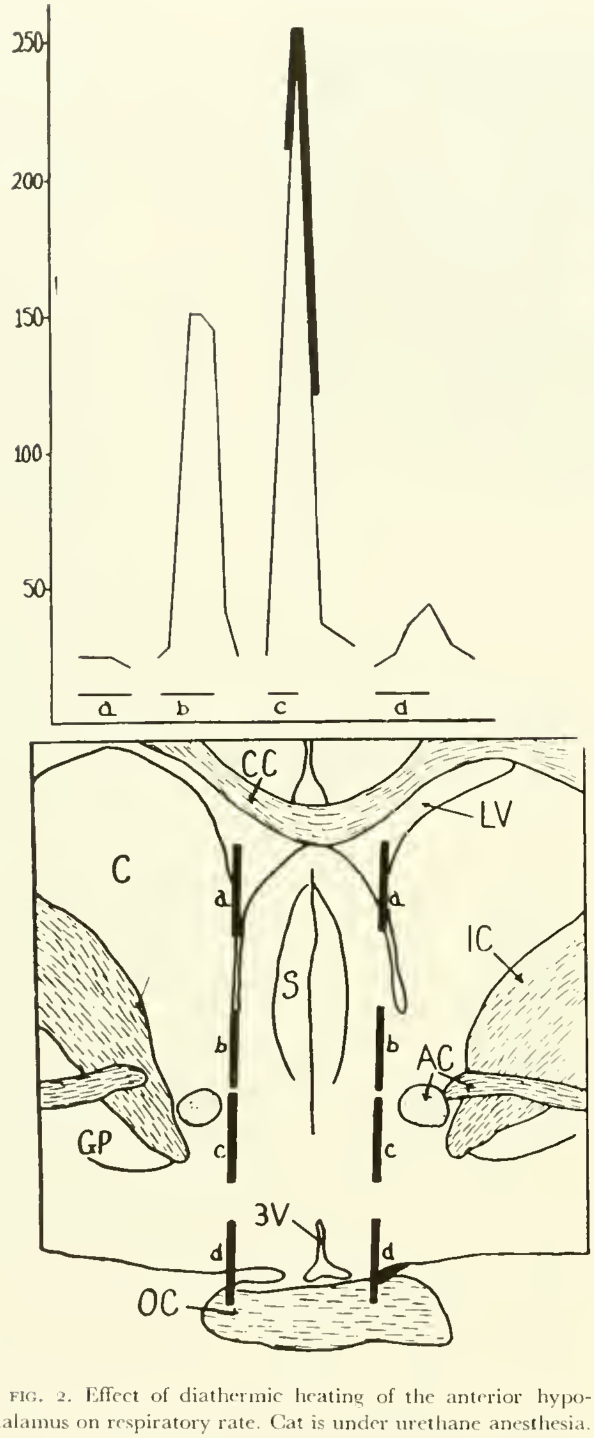

FIG. 2. Effect of diathermic heating of the anterior hypothalamus on respiratory rate. Cat is under urethane anesthesia. Heating is through two parallel electrodes with bare tips inserted by the Horsley-Clarke technique from above into the hypothalamus; electrode tip locations *a–d* are shown on *lower part* (schematic drawing of transverse section through a cat brain). Heating responses from locations *a–d* on respiratory rate are shown on *upper part* (breaths per minute on *ordinates*); *heavy line* indicates panting. *AC*, anterior commissure; *C*, caudate nucleus; *CC*, corpus callosum; *GP*, globus pallidus; *IC*, internal capsule; *LV*, lateral ventricle; *OC*, optic chiasma; *S*, septum; and *3V*, third ventricle. [From Magoun *et al.* (141).]

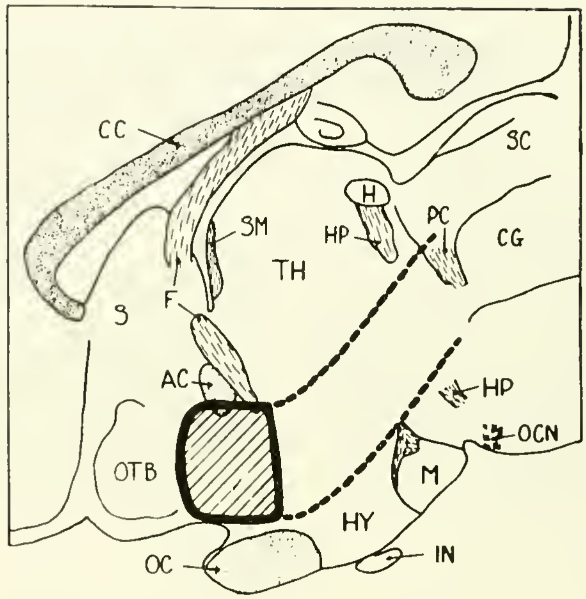

FIG. 3. Schematic outline of the region reactive to local heating, projected on a paramedian sagittal section through a cat brain. *CG*, central grey matter; *F*, fornix; *H*, habenula; *HP*, habenulopeduncular tract, *HY*, hypothalamus; *IN*, infundibulum; *M*, mammillary body; *OCN*, oculomotor nerve; *OTB*, olfactory tubercle; *PC*, posterior commissure; *SC*, superior colliculus; *SM*, stria medullaris; *TH*, thalamus; otherwise as in fig. 2. [From Magoun *et al.* (141).]

The thermosensitivity of the hypothalamus has been additionally confirmed in several other reports (63, 68, 101, 187, 189), extended to other animals, and obtained in chronic animals without anesthesia (101, 190). Warming of the hypothalamic thermodetectors in addition to polypnea and sweating also produces cutaneous vasodilatation (fig. 4). Inhibition of shivering also occurs if shivering is initially present, otherwise other signs of decreased skeletal muscular activity are evident. The result of hypothalamic warming is therefore a coordinated response of body temperature regulation, with activation of heat-loss mechanisms and suppression of the main heat-production mechanism.

If central nervous thermodetectors are to register central body temperature (e.g. the temperature of arterial blood in the aorta), they should be transfused by so rapid a blood flow that local heat production would not significantly influence the temperature around the thermodetectors. It therefore seems significant that the anterior hypothalamus has an abundance of capillaries, much more so than regions such as the posterior hypothalamus (65). The close proximity of the hypothalamus to the arterial circle

of Willis also seems to be of importance in this respect.

The suggestion that the medulla oblongata contains thermosensitive structures influencing cutaneous blood flow (13) and sweating (95) has not been substantiated.

Mechanism of Activation of Thermodetectors

The question has arisen whether the hypothalamic thermodetectors are sensitive both to warming and cooling, as suggested by early investigators (cf. figs. 4, 14). It should be remembered that the single unit response of the detectors has not yet been recorded. It is therefore not known whether a temperature rise which activates the heat-loss mechanisms produces an increase or a decrease (or perhaps both) in firing frequency of the first order neurons into which the detectors discharge (or which may be identical with the detectors). The surface thermoreceptors, the function and unitary responses of which are well known, may be considered analogous to the hypothalamic thermodetectors (103). Each surface receptor unit shows maximum activity (afferent firing frequency of the first order neuron) at an individually characteristic temperature. This temperature varies considerably within the family of receptor units. A rise of temperature is therefore accompanied by successive deactivation of some receptors and activation of others; within the normal range of body temperature the former may be classed as cold receptors and the latter as warm receptors. The only well-known property of the hypothalamic thermodetectors is that the range of temperatures within which the effector systems show prominent reactions, is relatively small, as suggested in figure 4, extending from perhaps 1 degree C below to a few degrees above the normal brain temperature (187, 190). At brain temperatures above 41 °C or 42 °C the effector systems may show reversal of reaction. It is possible therefore that the hypothalamic thermodetectors resemble surface warm receptors in having a temperature level for maximum activity slightly above normal brain temperature.

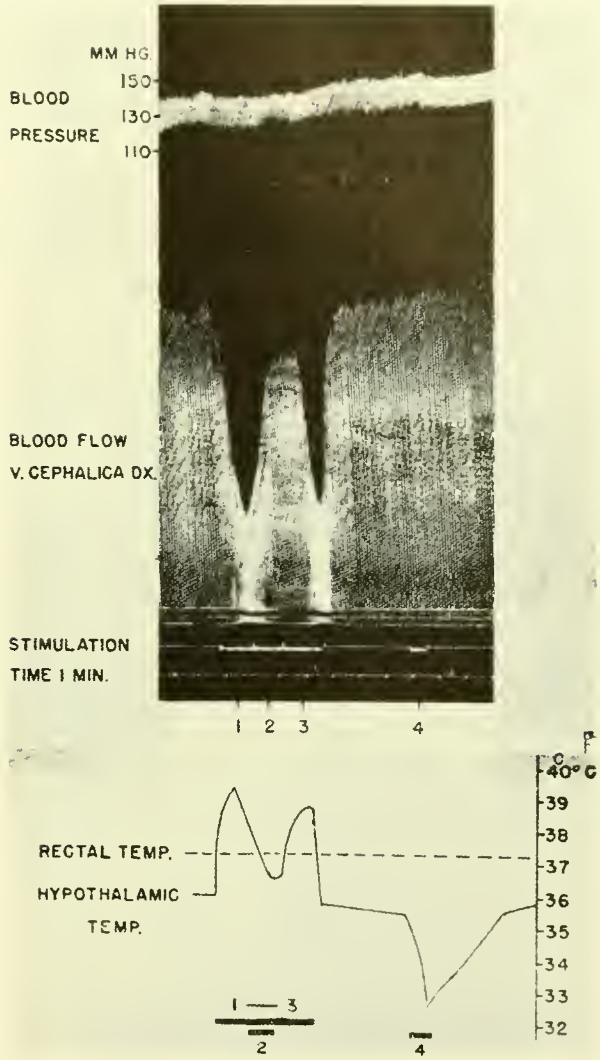

FIG. 4 Effect of diathermic heating and conductive cooling of the anterior hypothalamus on cutaneous blood flow. Cat is under urethane anesthesia with artificial respiration. Two parallel silver wire electrodes with bare tips, 4 mm apart, are inserted by the Horsley-Clarke technique into the hypothalamus. *Lower record:* Hypothalamic temperature measured by a thermojunction placed midway between electrode tips. *Upper record:* Blood flow from the skin of the forelimb pad measured by a drop interval recorder, ordinate height being inversely proportional to flow. Diathermic heating continuously from 1 to 3; conductive cooling at 2 and 4. [From Ström (187).]

The activation mechanism (mode of transducing thermal to electrical signals) of the thermodetectors is incompletely known but important information on this problem has been reported by von Euler (203, 204). When the brain is warmed via the carotid blood stream, a steady potential field is developed between the supraoptic region and the rest of the brain (fig. 5). The potential change, which may be as steep as 0.5 to 1.0 mv per 0.1 °C, is not produced by impulse firing; it may be analogous to the steady potential fields that can be registered in receptor structures with systematic spatial orientation, such as the retina, and may represent a 'generator potential' (the steady depolarization of receptors or of the finest terminals of first order afferent neurons which generate impulses in those neurons). It is interesting to note that a similar local steady potential field develops in the medulla oblongata when the arterial pCO_2 is changed,

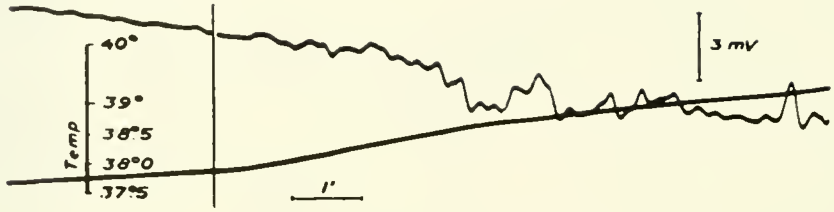

FIG. 5. Slow 'temperature potential' from the anterior hypothalamus. Cat is under urethane anesthesia. One calomel capillary electrode is inserted by the Horsley-Clarke technique into the hypothalamus; a slow potential (*upper curve*) was recorded against another electrode elsewhere in the brain. Hypothalamic temperature (*lower curve*) is recorded by a thermojunction. Brain is warmed by conductive heating of the intact carotid arteries. [From von Euler (203).]

a fact suggesting an analogy between central chemoceptive and thermoceptive structures (206). The structure of the medullary chemodetectors is as unknown as is that of the hypothalamic thermodetectors. This absence of histologically defined receptors is hardly more surprising for central receptive mechanisms than for peripheral receptors, such as those for pain.

It should be remembered that temperature changes influence all excitable tissues to a greater or lesser extent (28). Different types of peripheral nerve fibers show different thermosensitivity (137, 202). Local heating of mammalian C-fibers up to 41 °C or more depolarizes them and generates impulses, while cooling A-fibers has a similar effect. The central thermodetectors, however, seem to be more sensitive to temperature changes than are C-fibers.

CENTRAL INTEGRATIVE STRUCTURES

Effects of Stimulation

In 1884 and 1885 basal parts of the forebrain had already been suggested to influence temperature regulation by Ott (155, 156), and Aronsohn & Sachs (5) observed that mechanical puncture into the region of the corpus striatum in the rabbit is followed by a transient rise of body temperature ('heat puncture' or *Wärmestich*) with signs of increased metabolism. This observation is difficult to interpret in terms of normal physiology. The puncture probably produced an irritative lesion (120) near to (211) but not destroying those hypothalamic structures which later have been shown to contain a coordinating mechanism for the regulation of body temperature.

Electrical stimulation within the hypothalamus can evoke a multitude of responses. The skeletal muscular system (108, 111) may show increased or decreased tone either generally or in localized muscle groups. In the circulatory system (36) there may result increased sympathetic vasoconstrictor activity, either generally with resultant large increases of arterial blood pressure or in localized regions such as the skin; or alternatively decreased vasoconstrictor activity in the skin; or increased sympathetic vasodilator activity to skeletal muscle. Increased or decreased sympathetic accelerator activity to the heart may also appear, and increased activity of the adrenal medullae with augmented secretion of either epinephrine or norepinephrine (67). The respiratory system may show increased or decreased activity, e.g. apnea, hyperpnea, polypnea or panting (4, 109).

It is evident therefore that the main thermoregulatory effector systems can be influenced by hypothalamic stimulation. Such information does not define the quantitative role of the hypothalamic structures in normal temperature regulation, however. On the other hand, localized electrical stimulation in the anterior hypothalamus of an unanesthetized animal can evoke not only isolated effector responses but also a coordinated response of the main heat-loss mechanisms, i.e. panting, cutaneous vasodilatation and inhibition of shivering (figs. 6, 7), as demonstrated by Andersson *et al.* (4). Such a coordinated response has not been obtained from other cerebral regions, cortical or subcortical. The response is probably not dependent on cortical integration because chronic decortication does not markedly influence either a normally coordinated temperature regulation in the unanesthetized animal, or the individual effector responses to hypothalamic, electrical or thermal stimulation. The anterior hypothalamus therefore seems to be the location of a main coordinative mechanism which promotes heat loss, a conclusion which can also be drawn from results of chronic ablation experiments (see below).

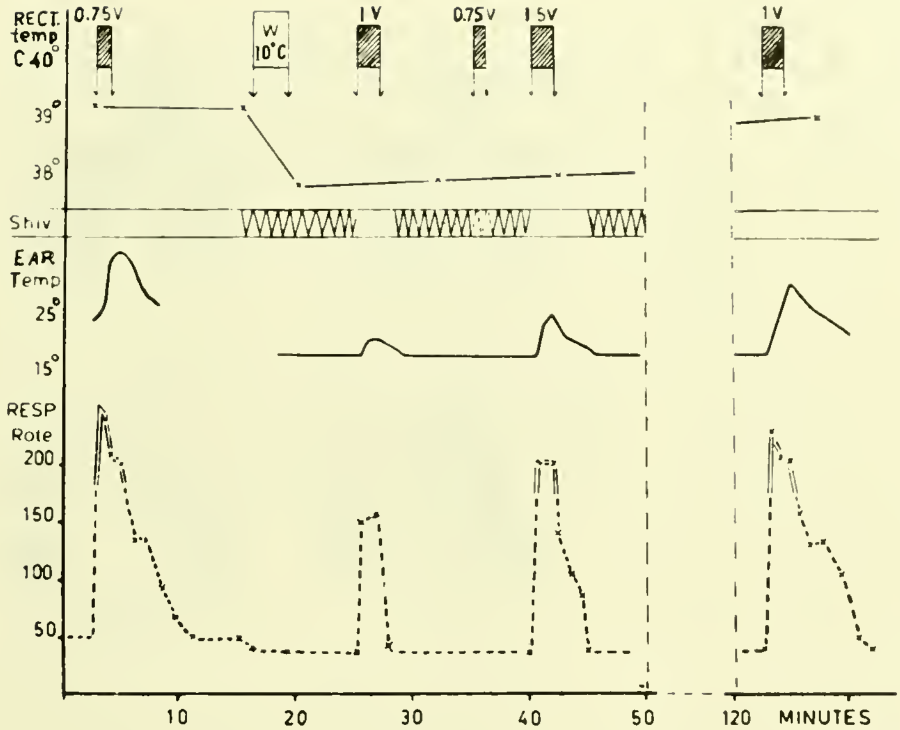

FIG. 6. Effect of electrical stimulation of the hypothalamic 'heat loss center' in the unanesthetized goat on shivering, ear temperature and respiratory rate. Electrodes are inserted by the Hess technique. Duration and voltage of stimulation are on *top*. *Double lining* of respiratory rate curve indicates panting. Body temperature was lowered at (*W*) by giving 3.5 l. of cold (10°C) water into the rumen; this induced shivering. [From Andersson *et al.* (4).]

Effects of Chronic Destruction

Chronic mesencephalic transection, caudal to the tuber cinereum, was found in 1914 by Isenschmid and co-workers (117, 118) to eliminate effective temperature regulation in the rabbit. A similar result in the cat was obtained in 1922 by Bazett & Penfield (22); it was also found in birds (178). Chronic high spinal transection in the dog was found in 1924 by Sherrington (181) to abolish thermoregulatory responses in the body region caudal to the transection level (fig. 8). Chronic partial or total decortication (117, 158), or even hemidecerebration (22), does not severely influence temperature regulation. The thalamus and the corpus striatum are not essential for a normal temperature regulation (21, 53, 147, 171), which is perhaps surprising since surface thermoreceptors probably project to the hypothalamus via thalamic relays (59).

In chronic experiments on cats and monkeys, Ranson, Magoun and co-workers (52, 170, 171, 191) showed that small lesions in the anterior hypothalamus (shown in fig. 9) reduce or abolish the thermoregulatory response to body warming (heat-loss mechanism), while lesions in the posterior hypothalamus also abolish the response to body cooling (both heat-loss and heat-production mechanisms).

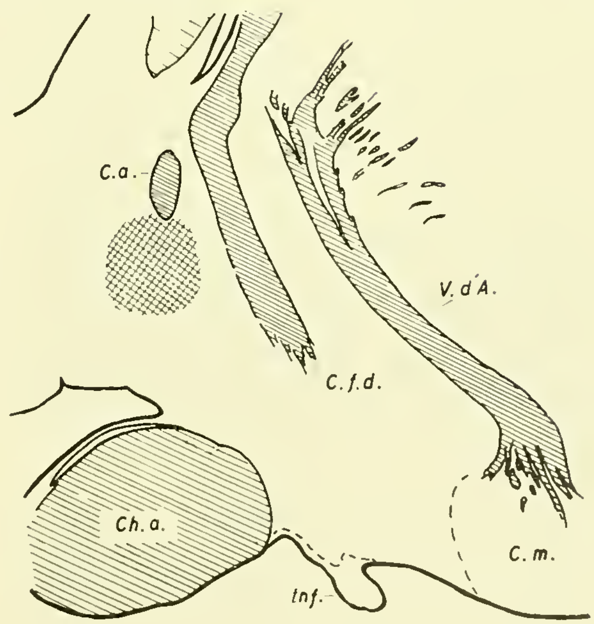

FIG. 7. Parasagittal section through the preoptic area and hypothalamus of the goat. Electrical stimulation in the *cross-hatched* area produces polypnea, vasodilatation in ears and inhibition of shivering in the unanesthetized animal. Application of electrodes is by the Hess technique. *C.a.*, anterior commissure; *Ch.o.*, optic chiasma; *C.m.*, mammillary body; *C.f.d.*, column. fornic desc.; and *V.d'A.*, Vicq d'Azyr's bundle. [From Andersson (4).]

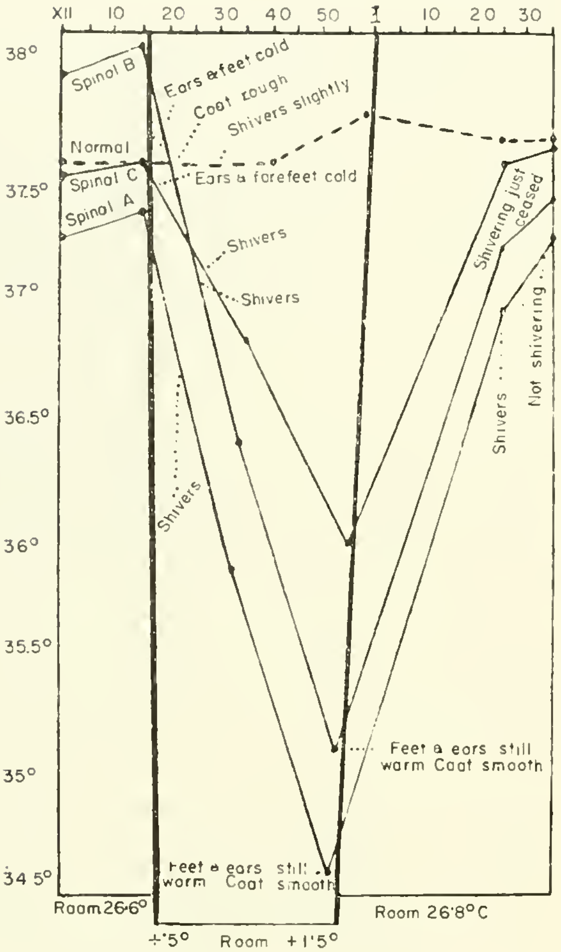

FIG. 8. Reactions of a normal dog (*interrupted line*) and of three spinal dogs (*solid line*) upon transfer from a warm room (+26.6°C) to a cold room (+1°C). Spinal dog *A* had a complete transection through the eighth cervical segment of 580 days standing; dog *B*, one at the eighth cervical segment for 40 days; dog *C*, one at the fifth to sixth cervical segment for 120 days. On external cooling, body temperature falls in the spinal dogs and muscles innervated by spinal segments cranial to transection exhibit shivering. [From Sherrington (181).]

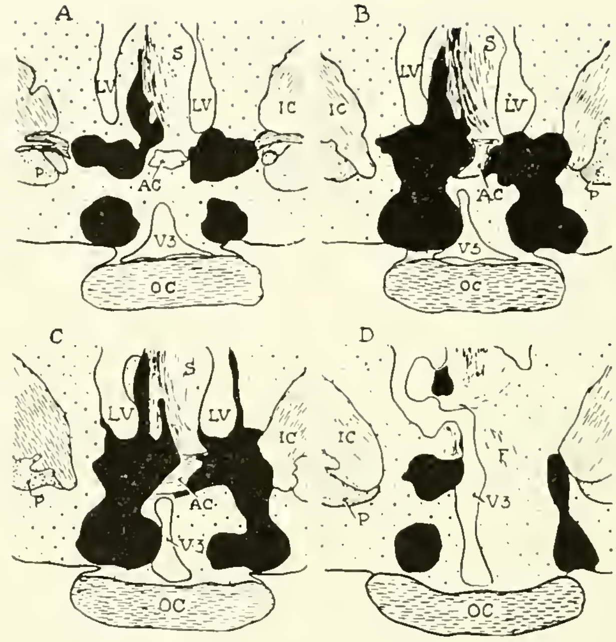

FIG. 9. Schematic drawings of four frontal sections (*A–D*, order of section caudalward) through the cat anterior hypothalamus, showing extent of chronic electrolytic lesions in a cat. After the lesion a hot box test produced an increase of rectal temperature to 41.4°C without appearance of panting. Abbreviations as in fig. 2. [From Clark *et al.* (52).]

This result has been interpreted as evidence for the existence of two anatomically separate coordinating 'centers,' one in the anterior hypothalamus regulating against body heating, the other in the posterior hypothalamus regulating against body cooling ('dualistic localization'). From a functional point of view, on the other hand, central nervous regulation of body temperature always involves reciprocal inhibition and facilitation of all the different thermoregulatory effector mechanisms in a quantitatively graded manner ('unitary function'). Experiments with chronic lesions have not revealed one definite cell congregation ('nucleus') or one specific pathway within the hypothalamus to be responsible for thermoregulatory mechanisms (52, 73, 186). Nor has it been possible to define such localization from the results of local thermal or electrical stimulation.

The main conclusions from these observations are *a*) that a thermoregulatory mechanism, which integrates information from surface thermoreceptors and central thermodetectors and coordinates the responses of the effector systems, is located in the anterior and posterior hypothalamus; and *b*) that no other such structure of similar importance exists in the central nervous system. The first of these two conclusions is generally accepted but the second is not. It has been suggested that the heat-loss coordinating mechanism (including the panting mechanism in the cat but not in the dog) is situated partly in the mesencephalon (30, 123, 124, 126).

Discrepant results have been obtained from experiments on animals with chronic high spinal transections (45, 119, 161). According to Thauer (192, 193, 195), spinal rabbits may regain a satisfactory temperature regulation if they are well kept for a sufficiently long time after the transection; according to other investi-

gators (74, 75, 133), such is not the case. Species differences may exist, as chronic spinal dogs apparently do not show active temperature regulation (45, cf. 193, however). If satisfactory histological control of the completeness of transection is made, a positive result of such experiments should weigh more than a negative result, as complications such as infection or bleeding locally around the transection, and perhaps undernourishment, imbalance of water and electrolytes, etc., may occur which can result either in a larger destruction than attempted or diminish the responsiveness of the thermoregulatory effector systems. The conclusion therefore should be that chronic spinal animals may regain some power of active temperature regulation, although ineffective in comparison to that of intact animals.

Chronic high mesencephalic transections have also been reported to leave traces of functioning temperature regulation (concerned with heat-loss mechanisms) intact, suggesting that structures caudal to the hypothalamus may have an integrative thermoregulatory function. A possible explanation for the discrepancy between the results of chronic hypothalamic lesions and chronic mesencephalic transection may be that in the former experiment cortical influences remain which are excluded in the latter. In evaluating these positive results of chronic transection experiments, their implication for normal temperature regulation should be judged cautiously. Even if central temperature regulation can be exerted to a measurable degree by spinal structures when they are freed from cerebral influence, their quantitative role in the intact animal remains unknown.

THERMOREGULATORY EFFECTOR SYSTEMS

Respiration

The respiratory system has pulmonary gas exchange for its main function, and both respiratory rate and depth are therefore mainly regulated to adapt alveolar ventilation to the metabolic needs of the body. In addition, dead space ventilation serves as an important thermoregulatory mechanism in most animals, heat load producing rapid shallow breathing, culminating in panting. These two mechanisms may conflict in the intact animal. A typical example is the increase in alveolar ventilation which occurs in anoxia and which decreases the ability of the body to preserve heat under cold stress (72, 76, 132). Another example is emotional or sexual activation which is accompanied by prominent respiratory reactions which can be seen in an exaggerated fashion in the chronic decorticate animal (17, 18). In man, the responses to overheating may induce true hyperpnea with increased alveolar ventilation and eventually hypocapnia and alkalosis (19).

Signals both from surface thermoreceptors and from central thermodetectors contribute to evocation of thermal panting; the quantitative importance of these two factors (32, 135) is difficult to judge and probably varies considerably between species. In some species, notably the dog, panting may start when the animal expects to start muscular exercise, when it is exposed to sunshine before body temperature rises (93) or when it is emotionally excited. Panting can also be evoked as an experimentally conditioned reflex (93). It may be concluded therefore that cortical mechanisms in some animals may incite panting. This is reasonable although it is difficult to elicit panting by electrical stimulation of the cortex. On the other hand, periods of panting unrelated to heat stress may occur in the decorticate animal which suggests that the cortex normally also exerts a modifying or suppressing influence. Decorticate panting may be dependent on structures in the dorsocaudal diencephalon (134) [although the evidence is controversial (53)] and may remain after ablation of the larger part of the hypothalamus (fig. 10).

Hypothalamic warming (fig. 2) and electrical stimulation (fig. 11) can produce panting. In the anesthetized animal it appears more easily when the respiratory resistance is low, as when the trachea is cannulated or when the mouth is kept open. It appears at a higher hypothalamic temperature than does cutaneous vasodilatation (fig. 12). After high mesencephalic transection, panting can only exceptionally be evoked (123, 154). Chronic hypothalamic lesions also extinguish the panting mechanism (fig. 13), even if the cortex is intact. The conclusion is that hypothalamic structures are the most important for the coordinated panting mechanism but that other structures (cortical, dorsal diencephalic) may also play a part by conditioning either the hypothalamic or the bulbar-medullary respiratory relays. In chronic spinal animals, panting occurs at a higher body temperature than in intact animals (35), illustrating the influence of the surface thermoreceptors which were deafferented by the transection.

Bulbar respiratory mechanisms are influenced by changes of body temperature, as is evident in animals with chronic mesencephalic transections (33), even

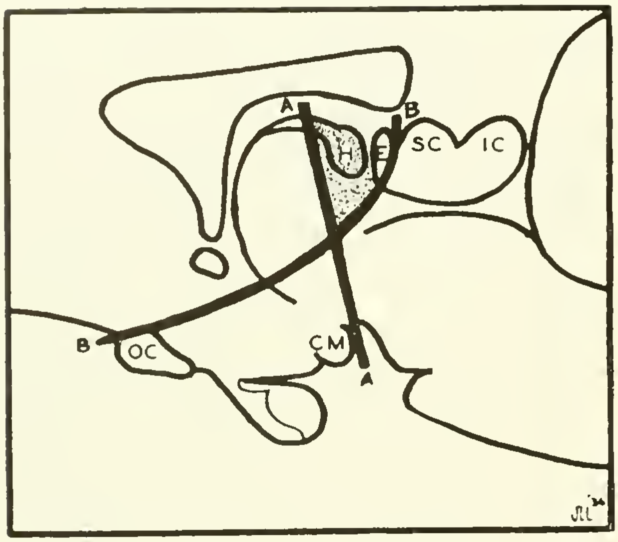

FIG. 10. Schematic drawing of sagittal section of a cat brain, showing (*dotted area*) the region found to be essential for decorticate polypneic panting. Transection *A–A* eliminates sham rage in the chronic decorticate cat; transection *B–B* eliminates decorticate polypneic panting. *CM*, mammillary body; *E*, epiphysis; *H*, habenular complex; *IC*, inferior colliculus; *OC*, optic chiasma; and *SC*, superior colliculus. [From Lilienthal & Otenasek (134).]

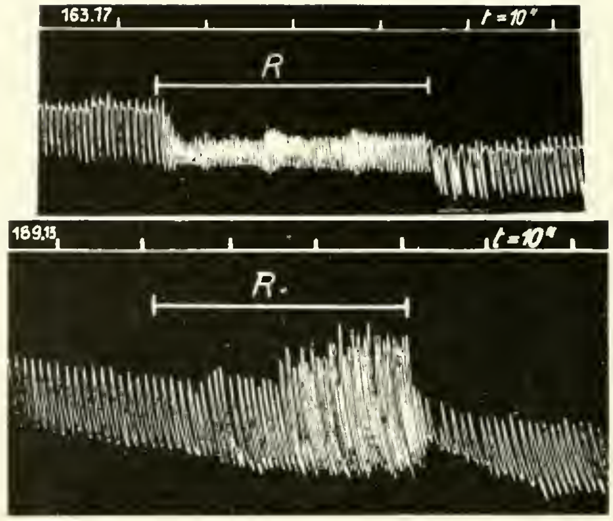

FIG. 11. Two types of respiratory responses to hypothalamic electrical stimulation (*R*) in an anesthetized cat. *Upper curve:* Rapid, shallow breaths (polypnea or panting) elicited from the dorsolateral region. *Lower curve:* Moderately rapid, deep breaths (hyperpnea) elicited from the dorsocaudal region. [From Hess & Stoll (109).]

if panting cannot result. In these animals polypnea results from body warming, but the increase in respiratory rate may simply be secondary to the simultaneous increase of tissue metabolism. Resting oxygen uptake of the whole body increases by about 13 per cent per degree C temperature increase, Q_{10} ranging from 2.6 to 2.9 (59), respiratory rate increases similarly, Q_{10} being 2 to 3 (34). If the carotid blood stream is heated, the carotid body chemoreceptors probably contribute slightly to the bulbar polypnea (29), although chronic denervation of the carotid body and sinus in the otherwise intact animal does not significantly influence thermal polypnea (197).

Depending on the nature of the stimulus which ultimately incites panting in the intact animal, one may speak of either reflex thermal panting in response to signals from surface receptors with unchanged brain temperature, or central thermal panting in response to signals from detectors activated by increased brain temperature. It is probable that reflex panting is reinforced by successively developed cortical conditioning (93).

Cutaneous Blood Flow

Changes of cutaneous blood flow produce skin temperature changes of similar direction, even if the two parameters are not linearly related. Cutaneous blood flow is therefore an important thermoregulatory effector system, influencing rate of heat loss from the body. In the unanesthetized animal, the degree of cutaneous vasodilatation depends on the coordinated reaction to signals both from surface thermoreceptors and central thermodetectors and from other mechanisms influencing vasoconstrictor tone. Vasodilatation is therefore not precisely correlated with any one of these factors, e.g. local hypothalamic temperature (71).

When an intact animal is warmed, the vessels of particular skin areas become dilated in a definite sequence, an observation indicating a regional 'vasomotor gradient' (115); this is related to a regionally different vascular sensitivity to such factors as the natural local hormones. Such thermoregulatory skin areas include parts of the face and the hands and feet in man (105), the ears and foot pads in the rabbit and the dog, and foot pads in the cat. They contain abundant arteriovenous anastomoses (50, 88). Blood flow through such a skin area can be varied within a hundredfold range (41, 43). Vasodilatation occurs

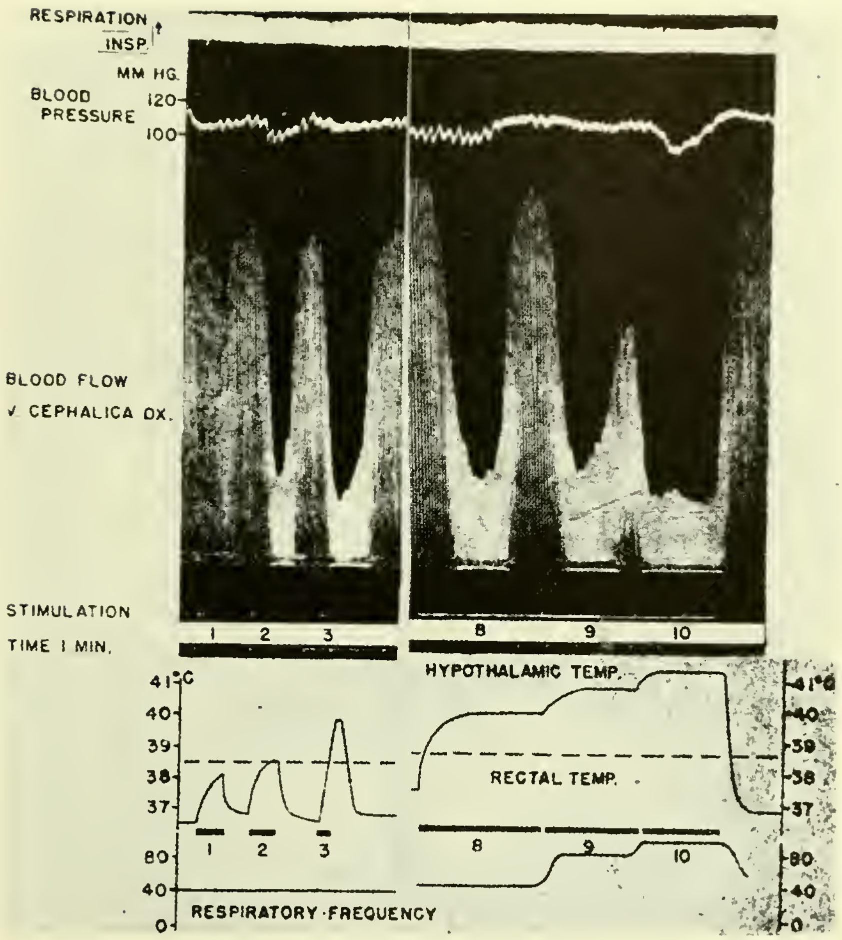

FIG. 12. Effect of diathermic and conductive heating of the anterior hypothalamus on cutaneous blood flow and respiratory rate. Cat is under urethane anesthesia. Experimental technique is the same as in fig. 4. Respiratory depth is measured by a perithoracic pneumograph. *1*, *2*, *8*, *9* and *10* signal diathermic heating; *3*, conductive heating. [From Ström (187).]

first in the face and ears, then in forelimbs or hands, and then in hind limbs or feet (7). Cutaneous blood flow is changed by variations of sympathetic vasoconstrictor tone (69); no unequivocal evidence for the existence in the skin of specific vasodilator fibers (sympathetic or dorsal root antidromic) has been put forward (70).

Local thermal stimulation of the anterior hypothalamus evokes cutaneous vasodilatation (as shown in figs. 4, 13, 14, 15) which appears within a few seconds of a steady warming and reaches an early maximum, then again diminishes or disappears. If the warming is more intense, the vasodilatation can be seen to remain to some extent during continued heating. This result can be expressed as a dynamic (transient) and a static (steady) response to a sudden and steady stimulus; in qualitative terms it resembles the afferent firing response from a surface thermoreceptor to a sudden temperature change. The vasodilator response also becomes apparent as a rise in skin temperature, with a certain time lag due to the heat capacity of the skin. The vasodilatation appears in the same sequence and with the same spatial gradient in the different areas of the body as during heat stress of the intact body. Unilateral hypothalamic warming gives a bilaterally similar response.

In the intact animal, the heat-regulatory responses of cutaneous blood flow are accompanied by converse changes in blood flow in deeper organs, such as the skeletal muscles (16) and viscera (80, 81, 174). Such a redistribution of blood flow between surface layers and deeper layers has obvious significance for arterial pressure homeostasis. It might theoretically be evoked either as a coordinated hypothalamic response or as a secondary effect of baroceptive reflex mechanisms. Local hypothalamic warming has given discrepant results relative to muscular or intestinal blood flow, some workers finding changes (182, 183),

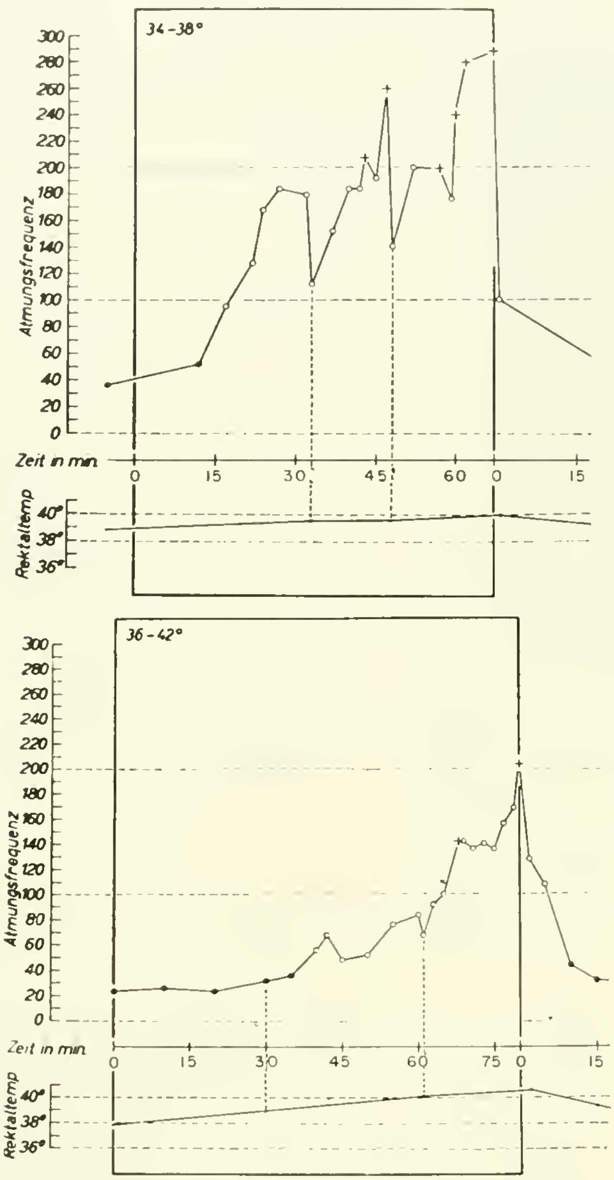

FIG. 13. *Upper part:* Increase of respiratory rate (*upper curve*) and rectal temperature (*lower curve*) in response to external body warming in intact cat. *Filled circles.* Normally deep breaths. *Open circles:* Shallow breaths (polypnea). *Crosses:* Shallow breaths with open mouth, moving jaws and salivation (panting). Room temperature was initially 13°C, within squared field 34 to 38°. *Lower part:* Effect of similar body warming in an unanesthetized cat 1½ mo. after bilateral electrolytic hypothalamic destruction. Drowsiness at start of warming is more conspicuous than in intact cats; eventual restlessness at end of warming is less marked. [From Hess & Stoll (109).]

others none (68, 187). In this situation, a positive result (a definite change) would weigh more than a negative one but it should be obtained in a cross-circulated region or in a baroceptor-denervated animal to be fully significant. Whatever the answer may be to this particular problem, the vasomotor response to local hypothalamic warming appears to imitate well the reaction of the intact animal to heat stress.

Mechanical stimulation of the hypothalamus may also influence cutaneous blood flow. Chronic hypothalamic lesions (129), as well as acute mesencephalic transection (189), produce cutaneous vasodilatation, an effect indicating that the thermoregulatory arteriovenous anastomoses in the skin are normally under tonic constrictor influence from the hypothalamus.

Electrical stimulation in certain cortical areas and notably in the hypothalamus influences cutaneous blood flow. Both vasoconstriction and vasodilatation may result, the effect depending on the one hand on the pre-existing vasoconstrictor tone, on the other hand on the frequency of stimulation (189). Reversal of effector response with change of cerebral stimulation frequency has been noted both for the circulatory and the gastrointestinal systems. One probable explanation is suggested by the observations of Pitts *et al.* (160) that electrical stimulation suppresses local spontaneous activity, probably by its synchronizing effect, so that low-frequency stimulation of spontaneously active neurons would result in a net decrease of output, while high-frequency stimulation of relatively inactive neurons would result in a net increase of output.

Electrical stimulation of the anterior hypothalamus, within the location of the thermodetectors, can thus evoke cutaneous vasoconstriction (189), but it can also evoke a coordinated heat-loss response in the unanesthetized animal, as shown in figure 6, including cutaneous vasodilatation, polypnea and suppression of shivering (4). Another more specific response can also be obtained, namely, a vasodilatation in skeletal muscles due to sympathetic vasodilator activity (62, 136), usually accompanied by cutaneous vasoconstriction. A variety of vasomotor mechanisms are therefore represented within that small region.

Peripheral thermoregulatory mechanisms, in addition to their local effect, can also influence the reactivity of the effector systems (188); thus, local cooling contracts blood vessels but also renders them unreactive to the central command.

Emotional elicitation of cutaneous vasodilatation may occur in man (blushing) which may interfere with thermoregulatory measures, although to a quantitatively insignificant degree. An analogous but more prominent reaction may occur in animals. The rabbit may react to stress by cutaneous vasodilatation

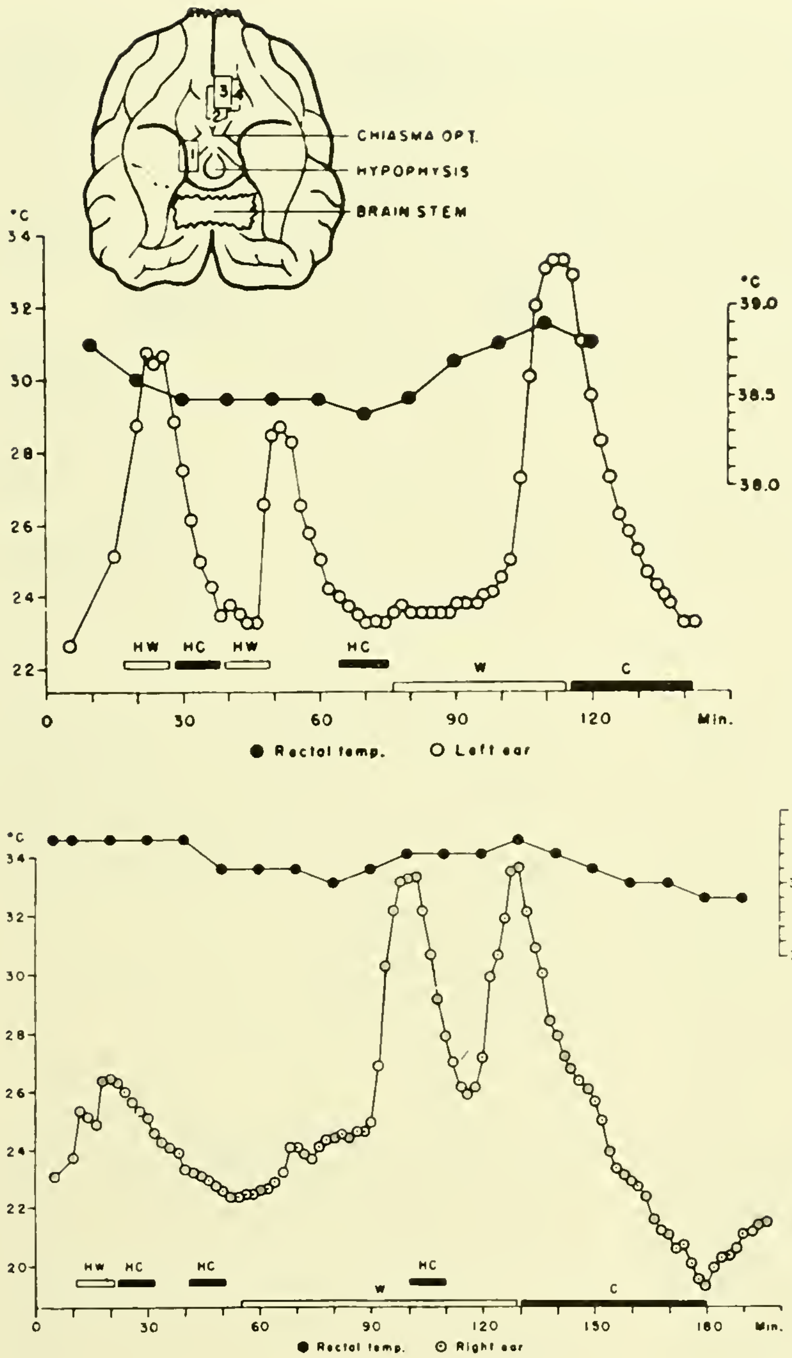

FIG. 14. Effect of warming (*W*) and cooling (*C*) of the hind limbs and of conductive warming (*HW*) and cooling (*HC*) of the anterior hypothalamus of an unanesthetized dog on rectal temperature and ear-skin temperature (reflecting cutaneous blood flow). *Inset* shows at 2 the localization of a hypothalamic silver thermode. Panting and shivering were elicited by *W* and *C* but not by *HW* and *HC*. [From Ström (190).]

which causes a marked and long-lasting fall in body temperature (85). A more significant interference with temperature regulation in man has been observed under psychopathological conditions. Schizophrenic patients may show abnormally large and irregular daily variations of body temperature (39), probably occurring as a result of both inadequate heat-loss control and heat-production activity. This abnormality may disappear after bilateral prefrontal lobotomy (40).

Sweating, Salivation and Piloerection

As examples of centrally evoked thermoregulatory effector responses, sweating, salivation and piloerection have been less studied than panting, cutaneous

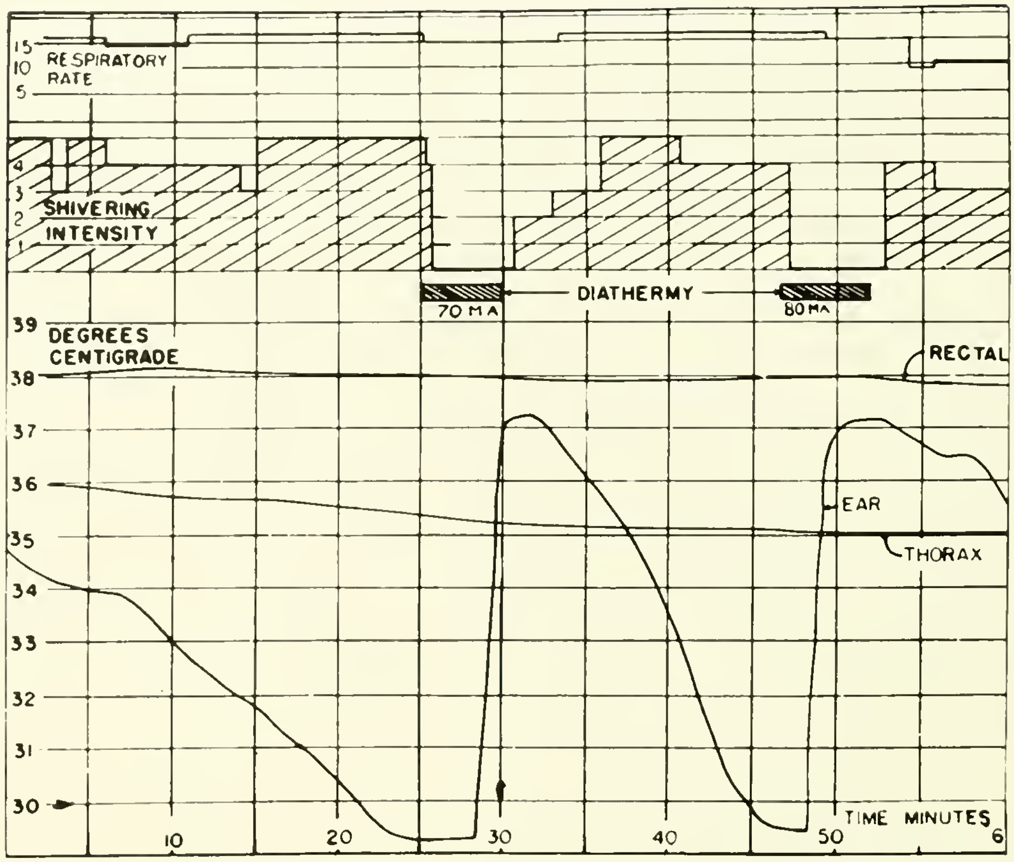

FIG. 15. Effect of diathermic heating of the anterior hypothalamus on respiratory rate, shivering intensity and ear-skin temperature in an unanesthetized dog. Heating is through a gold foil electrode chronically placed under the hypothalamus. The dog is under relative cold stress as evidenced by shivering and cutaneous vasoconstriction. Rectal and thoracic temperatures are also shown. Similar heating of the posterior hypothalamus resulted in drowsiness but did not influence shivering or ear-skin temperature. [From Hemingway *et al.* (101).]

vasodilatation and shivering. Sweating (165) may be elicited by hypothalamic thermal stimulation (94). It starts after a certain latency (26) as the skin has to reach a temperature of about 34°C first (212) and appears later than cutaneous vasodilatation and polypnea (26). Local injections of calcium and magnesium ions into the hypothalamus may suppress the sweating response (96); on the other hand, such injections also produce vasodilatation and fall of body temperature (131).

Increased salivation accompanies panting evoked by hypothalamic electrical stimulation.

Pilomotor responses (210) may be evoked by electrical stimulation of the hypothalamus in the unanesthetized animal, associated either with slowed respiratory rate and few somatic phenomena (from the anterior hypothalamus) or with increased respiratory rate, arterial pressure increase, and violent somatic phenomena (from the posterior hypothalamus). These two different patterns may perhaps be comparable to two naturally occurring reactions where pilocrection appears, the heat-preservation reaction, and the rage-fear reaction. Piloerection can occur in chronic decorticate animals and after anterior hypothalamic destruction but not after posterior hypothalamic destruction.

Shivering

Shivering consists of phasic skeletal muscular contractions, in man becoming apparent first in the head (masseter muscle), later in the arms, body and legs (200). In extreme shivering, the oxygen uptake may increase fivefold above the resting value (1). Shivering

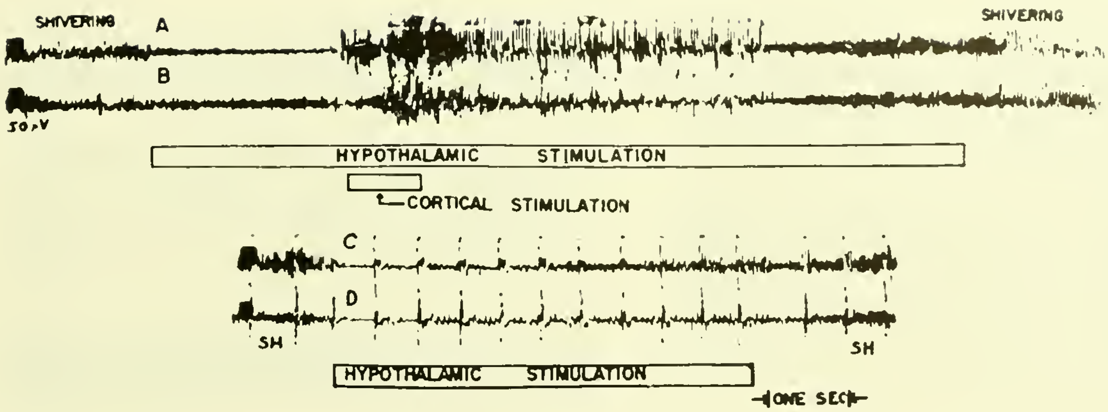

FIG. 16. Suppression of spontaneous shivering by electrical stimulation of the hypothalamus (electrodes inserted by the Horsley-Clarke technique). Cat is under light pentobarbital anesthesia. Shivering (*SH*) was recorded electromyographically by skin electrodes (*A* and *C*, thigh muscle; *B* and *D*, tail muscle). Hypothalamic suppression of shivering does not influence either cortically evoked muscular contractions (*upper part* of the figure), or the spinal reflex evoked by muscle stretch (*lower part*, stretch reflexes responsible for repetitive high voltage spikes). [From Hemingway *et al.* (100).]

becomes obvious in man when during cooling the central body temperature approaches 36.5° to 36°C (184), then increases at lower temperatures to a maximum at 33°C under light anesthesia (185). Shivering in man stops at a central body temperature just about or just below 30°C, in the rat at 16°C, and in hibernating animals at even lower temperatures (6°C). Hypoxia inhibits shivering (132). Shivering is obviously influenced by surface thermoreceptors (56) and by thermoreceptors in the tracheal mucosa (54) which explains the intensification of shivering during inspiration. It is also clear that local hypothalamic warming (101) and electrical stimulation (4, 100) which set a coordinated heat-loss mechanism into action can inhibit shivering (figs. 6, 15, 16) in an unanesthetized animal which has first been subjected to light cold stress to establish shivering. On the other hand, hypothalamic electrical stimulation can also produce shivering (2).

It is more doubtful whether local hypothalamic cooling, to levels well below normal brain temperatures, alone can evoke shivering in the unanesthetized animal which is in thermal balance (190) (fig. 14). Such experiments should preferably be made on unanesthetized animals (49, 132a, 190) as anesthesia suppresses shivering. If a dog with chronic high spinal transection (C_6 level) is cooled, the muscles innervated from above the transection exhibit shivering (fig. 8) in most cases (181) but not all (14). This response might be evoked either from brain thermodetectors or from those surface thermoreceptors (in the head skin, oral and nasal cavities) still in afferent connection with the cerebrum; the experiment therefore does not give definite evidence for either possibility. Stronger evidence for central elicitation of shivering is obtained if in similar experiments the local skin and brain temperatures are registered during the cooling (49). It has even been concluded that two types of shivering ('reflex' and 'central') can be separately elicited (49) and also distinguished by their patterns of appearance (139). On the other hand, local cooling of the anterior or posterior hypothalamus (fig. 14) has not been observed to evoke shivering in a thermally balanced animal (190), a fact suggesting that the hypothalamic thermoreceptive structures are relatively insensitive in the temperature range below normal brain temperature or, at least, have little effect in promoting shivering. As a negative result, however, this might be explained as due to recruitment of an insufficiently large number of central thermodetectors by the local cooling. In a careful series of experiments on dogs under light chloralose anesthesia, the brain was cooled via the carotid blood stream while the body temperature was kept constant (35a). The oxygen uptake, reflecting i.a. skeletal muscular activity, was found to decrease continuously with decreasing brain temperature under these circumstances. As the anesthesia caused only a partial and not a complete depression of the shivering response to whole body cooling, this

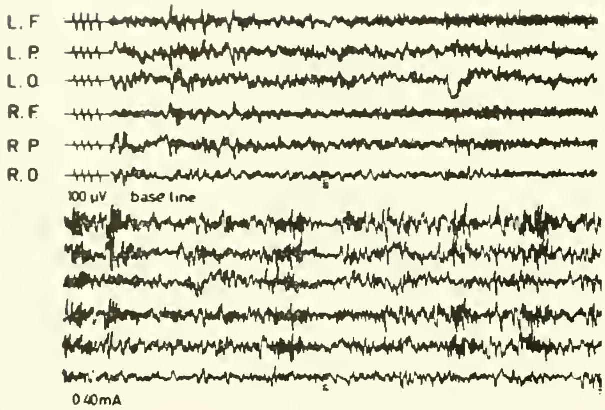

FIG. 17. Effect of hypothalamic warming (diathermic heating through two pairs of parallel electrodes with bare tips, inserted by the Horsley-Clarke technique into the anterior hypothalamus) on cortical electrical activity. *L*, left; *R*, right; *F* frontal area; *P*, parietal area; *O* occipital area. This is an unanesthetized *encéphale isolé* of a cat; the trigeminal ganglia are blocked by xylocain injections. *Upper part:* Before warming, asynchronous activity. *Lower part:* During warming to approximate temperature at hypothalamic heating electrode of 42°C, variable synchronized activity with 'spindles.' [From von Euler & Söderberg (208).]

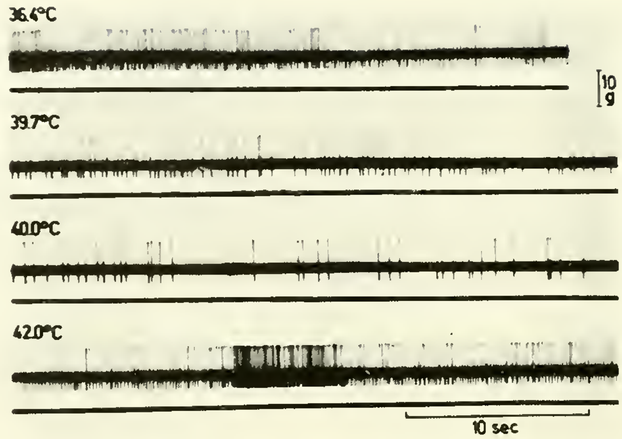

FIG. 18. Effect of hypothalamic warming (as in fig. 17) on the activity of the gamma-fiber motor system, as indicated by the impulse frequency in an isolated afferent nerve fiber from a gastrocnemius muscle spindle (*upper tracing*). Rabbit is under chloralose-urethane anesthesia. Hypothalamic temperature is recorded by a thermojunction placed at one heating electrode. Gastrocnemius muscle does not contract (mechanogram in *lower tracing*). [From von Euler & Söderberg (208).]

result can be interpreted as evidence that 'central shivering' is of little importance. The explanation for these apparently discrepant experiments becomes more clear if the problem is regarded from a quantitative rather than qualitative point of view in the following way.

An intact animal which is subjected to cold stress shows voluntary muscular activity and signs of alertness, even if shivering is not apparent. When it is slowly warmed to rectal temperatures between 37° and 39°C, the animal first becomes more less active, shows drowsiness and perhaps goes to sleep; but later when the rectal temperature increases even more and the heat-loss mechanisms have long since become intensely active, the animal again becomes restless. Moderate local hypothalamic warming can also produce drowsiness. This change in behavior has its counterpart in changes in activity of the cerebral somatic facilitatory or activating system, localized in the reticular formation in the brain stem, which has been described by Magoun and co-workers (150). This activity can be measured from cortical EEG changes (114), or from changes in the small-fiber motor system to skeletal muscle (gamma-fiber system) in the way suggested by Granit and co-workers (83), using afferent muscle spindle discharge as an index of gamma-fiber activity. Such experiments in cats and rabbits under anesthesia, and also on unanesthetized *encéphale isolé* preparations, have been performed by von Euler & Söderberg (207, 208). Local hypothalamic warming of moderate degree synchronizes the EEG (fig. 17) and simultaneously inhibits gamma-fiber activity (fig. 18); intense warming desynchronizes (arouses) the EEG (fig. 19) and simultaneously facilitates gamma-fiber activity (fig. 18), and it may also produce obvious restlessness in a superficially anesthetized rabbit. This result demonstrates the importance of the gamma-fiber system and the peripheral servoloop of skeletal muscle for the production of shivering, and explains why deafferentation suppresses shivering (157). A reasonable conclusion is that the hypothalamic thermodetectors project upon and to some extent modulate the activating system in the brain stem, thereby influencing wakefulness and skeletal muscle tone. An interesting further suggestion from these experiments is that the brain-stem activating system, which is mainly controlled by nonthermoceptive projections, may influence the activities of the thermoregulatory effector systems, including the skeletal muscles, as an independent reference mechanism (209). If such were the case, a certain change in the intensity of function of the activating system might balance the coordination of the different heat-loss and heat-production mechanisms at a new level of body (or brain) tem-

FIG. 19. Effect of hypothalamic warming (as in fig. 17) on cortical electrical activity from the left temporal area. Rabbit is under urethane anesthesia. Temperature of the hypothalamic heating electrode (*H.T.*), ear-skin temperature (*E.T.*) and respiratory rate are shown. Intense warming produces desynchronized cortical activity and 'emotional' polypnea, but no cutaneous vasodilatation. [From von Euler & Söderberg (208).]

perature. This might, e.g., explain why hyperphagia and a steady hyperthermia may appear together after hypothalamic lesions (145).

From a conceptual point of view this suggestion is a definite advance. The central nervous thermoregulatory mechanism has sometimes been compared to a thermostat; in fever and during hard muscular work (152) when thermoregulatory balance is achieved (20) at a higher level of body temperature than is normally the case at rest, the 'thermostat' is said to be 'reset.' A given intensity of muscular work leads in man to an ultimate new level of body temperature (152) which is relatively independent of the surrounding conditions for heat loss, an observation demonstrating that the body regulates by adjusting its heat-loss mechanisms at the new level. If under such conditions the activities of the different thermoregulatory effector systems can be stated quantitatively and the central reference mechanism, the brain-stem activating system, responsible for the new thermoregulatory balance can be defined, the terms 'thermostat' and 'resetting' would certainly have an explicit meaning.

Humoral Effector Systems

When a skin area is cooled, a reflexly induced activation of the adrenal medullae occurs with augmented secretion of sympathetic catechol amines (61). Intravenously administered epinephrine has a significant calorigenic (glycolytic) effect and has therefore been suggested to play a role in temperature regulation, but opinions differ as to its quantitative importance (138). Epinephrine and norepinephrine also constrict skin arterioles which would be an additional thermoregulatory effect, but the adrenal humoral control of peripheral vessels is quantitatively unimportant in comparison with their nervous vasoconstrictor control (42, 67). The adrenal medullae are under hypothalamic control but the possible coordination between adrenomedullary activity and the thermoregulatory effector systems is not well known (46).

Extirpation of the thyroid gland (119, 159), the adrenal glands or the hypophysis (31, 179) influences temperature regulation, reducing resistance to body cooling and the intensity of the fever response to pyrogens (77). This fact is not in itself sufficient proof that these endocrine glands take part in short-term temperature regulation in the intact animal. The extirpation effects might be attributed to a slowly changed reactivity of thermoregulatory effector organs, such as the blood vessels, to their normal mode of control. Direct evidence in acute experiments, however, demonstrates that exposure to cold within a few hours evokes an increase of thyroxin secretion from the thyroid gland of rabbits (37). After a further latency the metabolic rate of the body responds by an increase. This thyroid-activating effect of acute cold exposure is mediated via the hypothalamohypophysial connection (205). Local heating of the anterior hypothalamus has been reported to decrease the blood flow through the thyroid gland (183).

A relatively immediate effect on temperature regulation seems to be exerted by the adrenocorticotrophic hormone (ACTH) which induces hypothermia in the normal rabbit (fig. 20) and counteracts pyrogen fever (58).

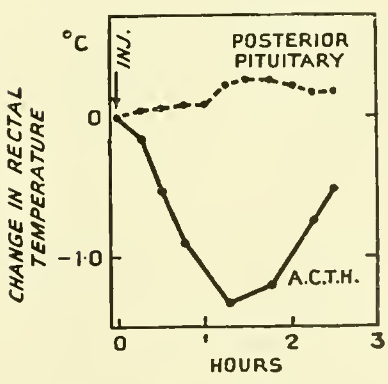

FIG. 20. Average change of body temperature in two rabbits after intravenous injection of posterior pituitary extract (0.1 units per kg) or adrenocorticotropic hormone (ACTH) (1 unit per kg). [From Douglas & Paton (58).]

The quantitative importance of endocrine modulation of temperature regulation is more indisputable when long-term conditions are considered. The resting metabolic rate and the microscopic structure of the thyroid gland vary with the time of the year in animals (but not in man); cold induces increased thyroid activity and this effect can be eliminated by hypophysial stalk section (199), a phenomenon indicating that it is elicited via hypothalamic structures as in the above-mentioned acute experiments. Another type of long-term adaptation of temperature regulation is the change in furring which parallels climatic changes in certain animals; this is also presumably centrally controlled and hormonally elicited. The process of hibernation represents the most extreme type of such adaptation.

An interesting example of changes in human temperature regulation occurring simultaneously with endocrine changes is the slight but relatively longstanding rise in body temperature which appears in women at the time of ovulation (19).

A specific thermoregulatory hormone produced in the thyroid gland and influencing tissue metabolism with short-term effects has been proposed (142, 143) but its existence has not been confirmed (153, 201).

Body Water Movements

As shown by Barbour (11, 14), body water movements occur during heat stress (hydremia with decreased diuresis) and cold stress (anhydremia with increased diuresis) (1). An anhydremic reaction is also seen in the beginning of fever and of muscular exercise when the body reacts as under cold stress until the body temperature has risen to a new balance level. The anhydremia or at least decrease of plasma volume in muscular exercise occurs rapidly, appearing within 5 min. of moderate exercise (112). In cold stress, water moves from the circulating plasma to the extracellular or intracellular spaces, particularly in the liver (12).

The water-shifting response to cold stress is dependent on the activity of the sympathetic nervous system and disappears after cervical spinal transection (14) or after adrenalectomy (11). Water shifting can be evoked by local thermal stimulation of the base of the brain in the rabbit; it disappears in animals with chronic destruction of the anterior hypothalamus (10, 11). The conclusion should be that the water-shifting response is at least partly evoked by the action of hypothalamic thermodetectors and is coordinated by anterior hypothalamic structures. Simultaneous changes of water excretion point to the participation of the supraopticohypophysial system in this pattern of regulation. Local diathermic warming of the detector region in the anterior hypothalamus may produce an immediate reduction of diuresis (183a), suggesting that this is a primary thermoregulatory effector response and not secondary to an increased water loss.

Cerebral and Spinal Pathways of Effector Systems

Unilateral hypothalamic stimulation produces bilateral responses from the thermoregulatory effector systems. Hemitransection at the pontine level eliminates contralateral sweating and diminishes ipsilateral shivering and piloerection in the whole body of the monkey (24). A similar effect is produced in the lower extremities by hemitransection of the thoracic spinal cord. The heat-loss effector systems project by pathways which, according to studies involving chronic lesions (25), can be anatomically separated from the heat-production system (shivering) as high as the mesencephalic level (125), the former being more medially situated than the latter. At the pontine level heat-production mechanism paths are localized within the cerebrospinal tract (127, 128) but, at the lower cervical level of the spinal cord, these two tracts are anatomically separated (48).

TEMPERATURE REGULATION UNDER ABNORMAL CONDITIONS

Effect of Anesthesia

The effect of anesthesia (99, 162) is to suppress temperature regulation, especially the cold response mechanisms. Anesthesia therefore usually leads to a slow fall of body temperature at effective surrounding temperatures below 34° to 35°C, the fall being proportional to the depth of anesthesia and independent of the nature of the anesthesia (fig. 21) (194). Magnesium ions have a similar effect (92). This rule has exceptions: small doses (light anesthesia) of pentobarbital inhibit the panting mechanism (140) and lead to increased body temperature in the cat (60), although not in the dog. On the other hand, the hyperthermia in cats produced by hypothalamic lesions is counteracted by pentobarbital (168). After the end of anesthesia, temperature regulation rapidly improves but does not become normal until after several hours (102). Ethyl carbamate (urethane)

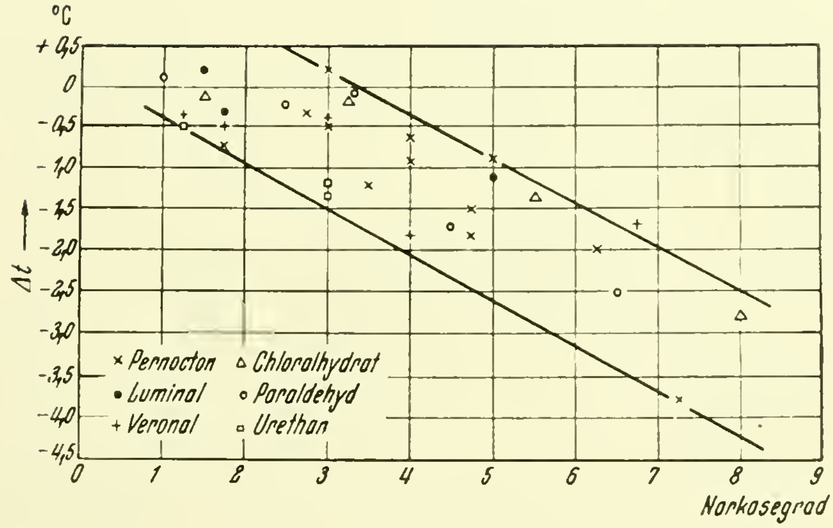

FIG. 21. Change in body temperature (*ordinates*) of anesthetized rabbits after 2 hr. at +19 C room temperature. Similar effect of different anesthetics; larger temperature fall at deeper levels of anesthesia (*abscissae*, arbitrary units). [From Thauer (194).]

administered locally in the hypothalamus in several animals, especially rabbits (131), or intravenously produces a rapid fall in body temperature (186); shivering is suppressed and heat-loss mechanisms are set into intense action, polypnea or panting occurring at subnormal body and brain temperatures (140). Local injections of drugs into the hypothalamus may produce hypothermia or hyperthermia (15). Chlorpromazine produces cutaneous vasodilatation but does not significantly inhibit shivering (47).

Fever

Since the early observation that mechanical stimulation of certain cerebral structures, later identified as the hypothalamus, may elicit a transient rise of body temperature ('heat puncture'), fever has commonly been regarded as evoked by an action of fever-producing substances (pyrogens) on the hypothalamic thermoregulatory structures. [These substances may also produce degenerative cellular changes in the hypothalamus (149).] A main theoretical reason for this conclusion would be that an approximately normal coordination of the different thermolytic and thermogenic mechanisms remains during fever (92, 203), although the body is balanced at a new and higher temperature, the body 'thermostat' being 'reset' at a higher temperature, otherwise functioning normally. Temperature regulation is not always coordinated in fever, however (84).

Hypothalamic lesions in cats have been reported to diminish or eliminate the fever response to pyrogens (169). Fever may, however, be elicited experimentally in animals with chronic hypothalamic destruction or in pontine or medullary (44) or even spinal (192) animals, indicating that the pyrogens, or rather the exogenous pyrogen plus the endogenous activated factor demonstrated by Grant & Whalen (87), may act at least partially on lower central nervous structures.

Hypothermia

Interest in the effect of drastic lowering of the body temperature (162, 185) has increased markedly since hypothermia proved to be a useful tool in certain surgical procedures, notably brain and heart operations. Shivering reaches a maximum at rectal temperatures between 33° and 35°C, as do also circulatory and respiratory reflexes (91). The relative influence of surface thermoreceptors and hypothalamic thermodetectors for thermoregulatory effector responses at these low temperatures is not definitely known, as discussed above. The influence of anesthesia is here put to practical use (130), certain combinations of anesthetics, muscular relaxants and sympatholytic agents being employed.

AGE AND SPECIES DIFFERENCES IN TEMPERATURE REGULATION

Ontogenesis of Central Temperature Regulation

The newborn animal does not possess fully effective temperature regulation. Regulation against cooling as well as warming develops rapidly, in the dog within 3 to 4 wk. (121). The effectiveness of human tempera-

ture regulation is related to postnatal rather than total postconceptive age, and rises rapidly after birth (37a). It has been proposed that the improvement in temperature regulation is correlated with the process of myelination of nerve fibers in the hypothalamus (38).

Phylogenesis of Central Temperature Regulation

The different thermoregulatory effector mechanisms vary in quantitative importance among different animal species. Piloerection is important in furred animals, and feather erection in birds. Sweating is less important in furred animals than in man, often being confined in the former to the foot pads. Such animals use panting plus salivation to lose heat by water evaporation.

Central nervous thermodetectors have been demonstrated in birds (177) and even in the turtle, a poikilothermic animal (175, 176).

Regulation in Intact Man

Although the existence of hypothalamic thermoceptive structures has not been directly proved in man, it is reasonable to assume that they do exist. The effect of bilateral frontal lobotomy indicates that the frontal lobe cortex does not play a prominent role in human temperature regulation. Mechanical stimulation of the hypothalamic region may cause transient hyperthermia (23, 66, 144). Tumors which destroy large parts of the hypothalamus may (57, 213) or may not (66) produce prominent disturbances of temperature regulation, with hyper- (3) or hypothermia. As such lesions are never strictly defined, and often are accompanied by destruction of other regions such as the hypophysis, the result is difficult to evaluate. The main trend of observations, however, strongly suggests (57) that hypothalamic structures are of similar importance for coordination of temperature regulation in man as in animals.

INTERACTION OF PERIPHERAL AND CENTRAL FACTORS IN TEMPERATURE REGULATION

The relative importance of surface thermoreceptors in comparison with central nervous thermodetectors in different homeothermic species has not been properly evaluated, but the principle of operation of such a double set of thermoceptive structures seems to be fundamental. The central thermodetectors reflect central blood temperature, being independent of thermoregulatory effector responses, while surface thermoreceptors reflect peripheral blood and cutaneous temperatures, being dependent on changes in

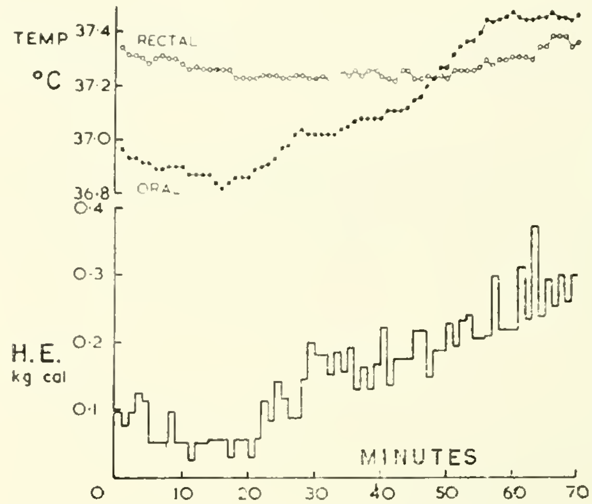

FIG. 22. Effect of external heating of one arm on rectal and oral temperatures, and heat elimination (*H.E.*, index of cutaneous blood flow) from the other hand in normal man. At the 10th min. external heating began and was slowly intensified. There is significant correlation between the rate of oral temperature rise and rate of heat-elimination increase, but no significant correlation between rectal temperature and heat elimination. [From Gerbrandy *et al.* (78).]

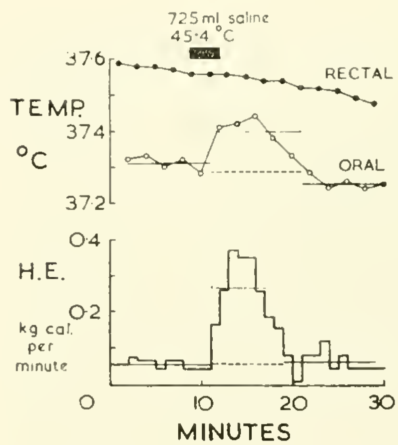

FIG. 23. Effect of rapid intravenous infusion of hot saline on rectal and oral temperatures and heat elimination from the hand (*H.E.*, index of cutaneous blood flow) in normal man. *Interrupted lines:* Mean control level. *Dotted lines:* Mean reaction level. There is a significant correlation between oral temperature rise (amplitude times duration) and excess heat eliminated, but no correlation with rectal temperature. [From Gerbrandy *et al.* (78).]

cutaneous blood flow and water evaporation. The two types of thermosensitive elements therefore have significantly different roles in regulation and supplement each other.

When cutaneous cold receptors are activated by external cooling, cutaneous vasoconstriction ensues as a regulatory measure. Skin temperature is thereby further lowered, and the cold receptors are still more intensely activated. This is a positive feed-back system which would lead to large oscillations of cutaneous blood flow in response to small stimuli unless modulated by an independent type of receptive mechanism working as a negative feed-back system. It is interesting to note that in some animals the skin areas of dominating receptive importance are not identical with those of dominating effector responses. This would diminish the positive feed-back tendency of the peripheral system (209). In man, on the other hand, these areas seem to coincide (69).

Another aspect of the interplay between surface thermoreceptors and central thermodetectors is illustrated by an old observation, which anyone can repeat, that heat-loss mechanisms which have been activated by a definite rise of body temperature can be suppressed by cold stimulation of a small skin area: the sweating evoked by a hot bath of long duration stops quickly when one hand is held in cold water (64). The generalized cutaneous vasoconstriction which rapidly follows local cooling of the hands leads to decreased heat loss and a definite increase of rectal temperature (6). If then the blood flow through the cooled extremity is suddenly increased, body temperature falls (because of redistribution of heat between deep and surface body layers) and shivering may start (82). In evaluating such observations it should be kept in mind that local skin cooling besides activating cold receptors also may evoke pain.

If the central body temperature is kept sufficiently high, cutaneous blood vessels remain dilated even at very low ambient temperatures (173). Different skin areas have different influences on central temperature regulation, the skin of the face being relatively most important (7). It also shows the quickest vasomotor responses in thermal stress. Localized warming of the skin, especially in the face, can evoke cutaneous vasodilatation (fig. 22) which by increasing the rate of heat loss lowers the body temperature until a new balance is reached (79). This explains the initial sensation of warmth when the face is exposed to the sunshine on a cold spring day, and the sudden chill and slight shivering which follow some quarter of an hour later.

Marked changes of thermoregulatory effector activities may occur with almost constant rectal temperature. As shown in figure 23, oral temperature is better correlated with such changes (55), a fact which reflects the dominating importance of cranial thermoceptive structures for the conditioning of central nervous temperature regulation.

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Regulation of feeding and drinking[1]

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CHAPTER CONTENTS

A DISCUSSION of feeding and drinking, of appetite, satiety, hunger and thirst, requires a knowledge of many other functions of the nervous system, and it may be well to note in the beginning that if certain other phenomena were better understood, a more adequate account of regulation of food and water intake would be possible.

SENSATION AND DISCRIMINATION

One of the important missing keys is a satisfactory theory of sensation in general. Sensations associated with hunger and thirst are so vivid and so universally known that they must be included in any explanation of feeding and drinking, and yet they cannot be explained nor can they be described very much better than Sherrington did in his essays on general sensation in 1900 (77). Although Cannon & Washburn (25), and Carlson and his associates (26) identified gastric contractions as the source of hunger pangs experienced in the epigastrium, while Cannon (24), Gregerson (40) and others have emphasized relative dryness of the oral and pharyngeal membranes as a stimulus for thirst sensation, the mechanisms by which these and other sensations are perceived remain unknown (in spite of careful investigations of sensory pathways of spinal cord and brain, as reviewed elsewhere in this *Handbook*). There is no hypothesis which explains in a quantitative way how the organism regulates either eating or drinking on the basis of sensory experience.

Sherrington's review contains another idea which is supported by more recent experiments, namely, there may be a type of perception taking place within the nervous system as a stimulus to eating or drinking. Sherrington wrote as follows: " 'Hunger' feeling (and 'thirst' feeling) are held, therefore, to originate in impressions elaborated by the bulbar centres receiving the roots of those [ninth and tenth] nerves. These centres are perhaps specially sensitive to those qualities of the circulating blood which depend on intake of food, much as the bulbar centre receiving the lung branches of the vagus is specially sensitive to the respiratory quality of the blood. It can hardly be supposed that in the nerve cells of these centres impulses are actually initiated by conditions of the blood supplied to them. . . . But the condition of their blood affects the excitability of nerve centres; it may be supposed to increase the excitability of those into which embouch the afferent nerves of the gullet and stomach. Some nerve centres are remarkably increased in excitability by moderate hunger, just as conversely the knee-jerks are found to be diminished

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after a heavy meal." In more recent studies the hypothalamus rather than the bulb has become the locus of the hypothetical actions by the blood, although Larsson (54) noted feeding after stimulation of the region of the dorsal motor nucleus of the vagus. Some of the most lively controversy in this field has arisen from attempts to identify the 'conditions of the blood' to which the hypothalamus responds. Meanwhile, Sherrington's question of whether changes in the blood can actually initiate nerve impulses remains unanswered.

There is now a tendency to use a measurement of food intake or water consumption as a criterion of the presence of hunger or thirst, in order to avoid the uncertainties of sensation. Data can be obtained which are fairly precise and also reproducible. This approach seems to be at least a modest step forward since only a few years ago these quantities were regarded as so unpredictable that their regulation was little studied. Credit for remedying this situation belongs in larger part to Gasnier & Mayer (35) and to Adolph (1, 2) who showed that food and water, respectively, can be treated in a quantitative fashion. Adolph's monograph encouraged other investigators to try to discover some of the causes of the apparent unpredictability in these regulations, and to endeavor to identify the regulating mechanisms. Fifteen years ago most animal rooms were not air conditioned so that fluctuations in environmental temperature affected feeding; the influence of the estral cycle was suspected but not established (21, 78); and the effects of changes in composition of the diet were almost unstudied from the point of view of their effect upon food and water intake (3, 84). When these and a relatively few other factors are controlled, a record of either food or water intake is a reliable guide to appetite or thirst if these phenomena are defined simply as desire for food or water. It is possible to measure also the rate of eating, frequency of meals and intervals between them (12). Experiments have been carried out upon normal animals in different environmental and metabolic conditions, upon animals with operations upon the nervous system and upon animals having electrodes or hollow tubes implanted in the brain for study after recovery from the effects of anesthesia.

Most of the experiments on the nervous system have been done to measure total food or total water intake in animals fed standard diets. They offer little understanding as to just how hunger differs from thirst except that one is a response to deprivation of food, the other to lack of water. We know only from personal experience that one seems referred to the epigastrium and the other to the mouth and pharynx. Animals do not always distinguish between the two states; thus, a newborn mammal obtains water and food simultaneously in the mother's milk and, presumably, has no need for separation of hunger and thirst. The capacity to discriminate between the two appears in infancy, since Cooke found evidence of it in babies of 3 mos. and older (27). Even more complex and uncertain is the ability of animals to make a selection among diets of distinctive composition (74, 75) and among the 'specific' hungers, of which salt hunger is believed to be a prominent example. How the body 'knows' that it needs protein rather than carbohydrate, carbohydrate rather than fat, a diet containing a particular vitamin or amino acid rather than a deficient diet, or, for that matter, food rather than flavored sawdust, is a mystery.

BEHAVIOR, COMPARATIVE ETHOLOGY AND PSYCHOLOGY

Both feeding and drinking require behavior movements more complex than those of simple reflexes. If all of the data relating to feeding behavior of higher animals (including the traditions of animal husbandry), and all psychological studies where hunger, appetite, satiety or thirst are important variables were to be reviewed, the result would be a large encyclopedia. Included would be not only food acceptance, but searching, recognition and discrimination, in addition to practically innumerable studies of motivation and aggression, as well as the problems of innate behavior, instinct, learning, memory, conditioning habit and prejudice (14, 44, 79, 87). In brief, if feeding and drinking could be explained, some of the most important questions in neurophysiology and psychology could be answered at once. The present review is incomplete in that it does not explore the neurological basis of nursing, chewing, swallowing, nor processes concerned with rumination and other similar activities; it gives slight attention to grazing, pursuit, fighting, hoarding and maternal behavior in feeding the young; it hesitates to mention the possibility that even the most complicated of activities, man's labors, trades, professions and even wars have reference in some way or other to urges to eat and drink. Food is, without any doubt, the oldest and most widely used 'tranquillizer.' This subject is no small one; adequate study will provide a tremendous quantity of interesting and important data.

SIGNIFICANCE OF NERVOUS SYSTEM

Two of the more enlightening discussions of hunger and appetite, those of Carlson (26) and of Adolph (3), begin and conclude, respectively, with the idea that feeding is an activity of all animals, including those having no central nervous system. Adolph wrote (p. 124): "All animals that have been studied, those without alimentary tracts as well as those which have, recognize food, spurn food when it is superabundant, and put forth extra efforts to get it when it is rare. Hence, whatever be the machinery that may fix the pattern of priorities in rats, comparable patterns seem to be endowments of all animals, whether or not they possess specialized neuromuscular or alimentary systems." It seems possible that study of these phenomena in higher animals might progress more quickly if more were known about the behavior of lower forms, including those possessing no central nervous system.

The relative significance of a given portion of the nervous system, for example, the hypothalamus, may be evaluated by asking which animals have this part of the brain. According to Crosby & Woodburn (29) the hypothalamus is well developed even in cyclostomes. [Insects and other arthropods have ganglia that may serve some of these same functions.[2]] One cannot say whether the development of this part of the brain is to be regarded as advanced in lower animals or as primitive in man. The fact that it is similar throughout the series of vertebrates suggests that it serves activities common to all of them and leads to a desire for more information on feeding mechanisms and behavior from the point of view of comparative physiology.

In contrast to the relative simplicity of the hypothalamus and its uniformity among vertebrates are the specialization and complexity of higher parts of the brain. As in other forms of behavior, the functions of the cerebral cortex in feeding are probably more evident in man than in lower animals, yet in man they are most difficult to analyze. Basic mechanisms seem often to be obscured by habits, customs and prejudices that a physiologist has no way to study. Perhaps the adult human brain should be put aside for the moment in order to study the nervous system of babies which is simpler in both organization and function. In a baby nursed only by his mother, the regulation of feeding and drinking is probably as straightforward as it can be in a human situation (27). The behavioral responses of babies include the sleeping-waking cycle, crying, general movements of body and extremities, and basic feeding reflexes allowing them to locate the nipple, grasp it, suckle and swallow. They definitely exhibit appetite and satiety. The regulating system, of course, includes the mother, since the amount of milk the baby gets is a function of the rate of milk production, amount stored in the breast, and activity and duration of activity of mechanisms making it available to the baby, e.g. milk ejection. That these are present in other mammals may encourage a comparative study. These advantages seem so obvious that one asks why more studies have not been done. There are at least two reasons: pediatricians in hospitals usually do not have the baby's mother present to complete the regulating system; and physiologists observing a baby in their own family sometimes have difficulty in remaining objective about the situation. When, rarely, a first-hand report does appear, it may have the interest and clarity of the papers by the Newtons (68, 69); they studied, however, the maternal side of the regulating system. To encourage further research an environment like the one said to exist in nursing homes in England seems to be desirable. There an experienced mother nursing at least her second child, free from cares of the rest of the family for possibly 3 weeks, could provide data to answer many questions. Related experiments, of course, can be and have been performed in laboratories and at agricultural experiment stations; but their goal has been, so far as I can learn, to discover how to make the offspring grow the most rapidly or how to obtain a maximal milk production. The same techniques should be suitable for studying, rather, the organization of the regulating systems.

INTERRELATIONSHIPS AND INTEGRATIONS

Regulation of food and water intake are examples of the integrative activity of the nervous system — integrations more complex than those of the reflexes in Sherrington's classic monograph. When the integration is considered only in a quantitative sense of how much food or water is taken, the part of the

[2] In addition to earlier papers by Dethier (31), a more recent account of his experiments reveals that in blowflies feeding on sugar solutions, two mechanisms are important. One is the taste of the solution; the other is the degree of distension of a certain part of the foregut. On the basis of these two mechanisms Dethier & Bodenstein have explained the quantitative features of feeding activity in flies (30a). They are the first authors to have achieved this goal using any animal.

brain most definitely involved is the reticular formation of the brain stem and the hypothalamus. In their representation within the brain, hunger and thirst are related to other phenomena such as posture and locomotion, control of pulmonary ventilation, the sleep-waking cycle and regulation of body temperature. All of these appear to be regulated by mechanisms of the general class of controls systems—systems which are analyzed by engineers using techniques derived from information theory. This type of study is difficult in biological systems and has not as yet been developed fully for any one regulation. As a way of thinking about these phenomena, it seems to offer the advantage of a hope of mathematical analysis, and it also encourages the study of a regulation by means of analogy with a system better understood. As Sherrington mentioned, a useful analogy is control of pulmonary ventilation, since it has many characteristics in common with regulation of eating and drinking (77). Like breathing, feeding and drinking are periodic and rhythmic phenomena, subjected to reflex control, with integration and possibly 'motivation' from the brain stem. All levels of the nervous system, including the cerebral cortex, take part in the regulation. The quantities regulated—minute volume and food or water intake, respectively—are in each case the product of a frequency multiplied by a quantity. Respiratory minute volume is the product of tidal air multiplied by respiratory rate, while food intake is a product of frequency of feeding and size of meals. In the brain stem the inspiratory and appetite centers are analogous, while the expiratory and satiety mechanisms appear to be similar. Both regulations have their central mechanisms of control, yet they are each affected by specific reflexes from particular organs. For example, reflexes from chemoceptors and from stretch receptors in the respiratory tract are important in respiration, while reflexes beginning with olfaction and taste, together with those from receptors in the wall of the digestive system, take part in the control of feeding. The inhibition of feeding when the stomach is distended may be analogous to the inhibition of inspiration when the lungs are stretched, the Hering-Breuer reflex. And finally, both of these regulations are associated with painful sensations designated as hunger, e.g. air hunger. It is necessary to point out that study of pulmonary ventilation has gone forward with little attention to air hunger. As painful and as dramatic as this sensation may be, it does not appear in the present-day schemes of the control of respiration; its function may be limited to periods of exceptional respiratory need. Whether gastric hunger is similar in its significance is not known. It is possibly most important in babies where the crying it causes helps to secure for the infant his mother's attention when food is needed.

In control of pulmonary ventilation the respiratory minute volume is regulated by way of the arterial tension of carbon dioxide, the pH of arterial blood and, apparently under unusual circumstances, by the oxygen tension. Students are often surprised to learn that a process so essential to life as is the supply of oxygen should be regulated, almost incidentally as it were, through control of carbon dioxide export. A similar situation exists for feeding mechanisms; although the end result of regulation is control of energy intake, animals apparently have no mechanisms for measuring energy per se. They do not meter calories ingested but attain energy balance indirectly through reactions that are related to or proportional to energy need. The several hypotheses put forward to explain this are reviewed later.

Adolph (3) seems to have introduced into the literature of this field the idea that animals show priorities, competition and compromises in their regulation of the several variables contributing to homeostasis. Considering the regulations where the tegmentum of the brain stem plays a part, one can say that pulmonary ventilation has first priority, then body temperature, body water and energy intake, in that order. The exchange of respiratory gases must be regulated almost from moment to moment, and errors, especially for oxygen, cannot be tolerated for the convenience of some other regulation; there is little inertia in the system for oxygen because of small stores within the body. Heat exchange is less demanding, especially in larger animals where heat content of the body offers inertia in the direction of both gain and loss; errors are corrected in minutes or hours, in small or large animals, respectively, and rate of production can be balanced against rate of loss to compensate for limitation of one or the other. For water exchange the correction may require up to a day or longer; in man a load or deficit can be tolerated for days, and panting animals incur dehydration to prevent overheating. With respect to food intake and energy balance even longer intervals are possible, and balance is readily sacrificed to maintain either body temperature or pulmonary ventilation, or even to accomplish muscular exercise. These are not independent variables in a rigid hierarchy, as one can see by observing changes in ventilation accompanying or even necessary for eating and drinking. This competition among regulations and the influence of one regulation upon

others offers an opportunity for studying the functions of the brain stem in a manner not revealed by analysis of any one regulation alone.

Another type of interrelationship deserves mention. Food intake is not an independent variable in energy exchange, since it is the source of all the energy animals have available for heat production, work and storage either as growth or fatness. The common knowledge that body weight of adult subjects tends to remain constant is evidence that there is regulation of the four variables as well as of each one, alone. In other discussions of this subject the hypothalamus has been proposed to be the part of the nervous system responsible for the 'automatic' features of the regulation of energy exchange, and heat production has been suggested as the common denominator between food, work, storage and temperature regulation (18, 80). These conclusions are based upon reports that lesions in selected regions of the hypothalamus may alter food intake (6, 20), body temperature (73), body weight or spontaneous activity (43, 57), and also upon evidence from normal animals revealing changes in other variables when one of them is arbitrarily changed by the investigator. The idea that the hypothalamus integrates these regulations, although hypothetical, seems to be generally accepted. It is being studied further in the laboratory by examining the effectiveness of temperature regulation in animals with disorders of feeding, and by searching for other possible correlations between deficits of regulation of activity, food intake and heat exchange.

LEVELS OF NERVOUS CONTROL

Our present understanding of how the nervous system achieves the regulation of feeding and drinking may be summarized in a few paragraphs. In higher animals the brain stem, including the nuclei and primary connections of the cranial nerves, is the level most directly concerned. The basic patterns are probably reflex in nature, requiring integrated motor activity of trigeminal, facial, glossopharyngeal, vagal and hypoglossal nerves, while the sensory components of these as well as many other nerves are playing their part. For almost any animal, including one which has just eaten, food is a stimulus for these reflex responses; when there occurs an adequate sensory stimulation, animals move toward food, investigate, eat and swallow it. Reflexes of attention, approach, examination, incorporation and rejection appear to be important. Little is known of these mechanisms, however, and it is not clear just how much of feeding behavior can be designated as reflex and how much may be either conditioned responses, learned behavior or some other type of more highly organized activity. It seems desirable to attempt to learn more about these reflexes because neurophysiology has so often gone forward by way of study of reflex mechanisms.

Pertinent data have been obtained from studies of the behavior of animals with lesions at selected levels of the neuraxis, and of unanesthetized animals during stimulation or perfusion of discrete areas within the brain. Experiments by Miller & Sherrington (62) and by Bazett & Penfield (15), using decerebrate cats, showed that simple feeding responses are possible after removal of much of the mesencephalon and all of the more rostral portions of the brain. Their decerebrate animals were capable of reflex chewing and swallowing and of reflex rejection of certain materials. Bazett & Penfield noted purring after their cats were fed which suggests that a certain degree of 'satiety' can occur even at the reflex or segmental level. (Sherrington's reference to 'spinal hunger' is found below.)

The function of the hypothalamus, the next higher level, is assumed to be quantitative, as already stated, as if this part of the brain adjusts energy intake to expenditure. The medial hypothalamus is believed to take part in reactions of satiety, while the lateral portions are responsible for appetite. After destruction of the lateral regions, animals fail to eat (6, 33); in some cases the failure persists until death, in others it is transitory or may be relieved following a period of artificial feeding (8, 67, 86). Medial lesions, by contrast, lead to overeating and obesity in all species studied including man (20, 22).[3] When the lateral mechanism is stimulated in unanesthetized animals, feeding occurs (7, 23, 30, 53). Stimulation of the medial region, as well as of certain other portions of the brain, induces what appears to be satiety. This was discovered by Olds (70) and others have confirmed his observations. In theory, the interaction of these two hypothalamic regions might account for most of the quantitative aspects of regulation of food intake, since the cerebral cortex and other locations in higher levels might affect the appetite via the hypothalamic mechanisms. This, however, is not known and is not necessary, since the cortex might act upon

[3] A convenient means of destroying these regions in mice is by the intraperitoneal injection of gold thioglucose (56, 58). The resulting obesity is like that of animals with lesions produced in the hypothalamus by electrolysis (32, 54).

feeding reflexes directly or through the reticular formation. It is conceivable that the lateral hypothalamus or appetite mechanism serves to facilitate the feeding reflexes, while the medial hypothalamus or satiety mechanism acts to inhibit the reflexes. In a fasting condition the lateral portion would be active, the medial one quiet, with a resulting high appetite and low satiety. But after feeding the lateral portion would be quiet and the medial one active—low appetite and high satiety. When the medial mechanism is injured and hyperphagia follows, any remaining regulation probably occurs through variations in activity of the lateral portion, that is, through changes only in appetite. This may explain why food intake is so labile in animals with hyperphagia, as Kennedy (49), Stevenson (63) and Teitelbaum (85) have observed.

The highest level of the brain, the cortex, is also involved in feeding responses, as the early paper by Paget (71) and the later review by Kirschbaum (51) emphasize. There are, however, not many experimental data relating to this subject with the exception of certain psychological studies on animals, especially primates. Observations by Pribram & Bagshaw (72) using monkeys imply that the cortex is necessary for recognition of objects suitable for food and for feeding responses determined by social environment. Since the work of Goltz (38) it has been known that decorticate animals are restless at feeding time and quiet after they are fed (76). Similar observations have been made upon infants born with cerebral lesions or an imperfectly developed brain. If the lesions are confined to the cortex, the babies seem to have little difficulty in nursing. Indeed, even in normal infants there is no reason to suppose that feeding requires the highest levels of the nervous system. Later, as more complicated behavior patterns appear, the cerebral cortex is more definitely implicated.

CENTRAL PERCEPTION

All of the prominent hypotheses regarding regulation of feeding and drinking are alike in that they assume that the brain, probably the hypothalamus, contains sensitive or 'sensory' elements capable of responding to the 'qualities of the circulating blood' mentioned by Sherrington. Among the qualities or 'signals' proposed are water concentrations (9, 48), availability of glucose (59, 60), metabolites related in concentration to the size of bodily reserves of fat (50) and thermal gradients (18, 83). Although certain authors have been inclined to look upon some one of these as the basis of the regulation of, for example, feeding, others have decided that multiple factors are responsible for the transition from appetite to satiety (5, 18, 46). Of the changes mentioned, there is little question that animals are hungry when the brain is lacking in carbohydrate supply, as it is during insulin hypoglycemia; but if a lack of available glucose is to be used to explain the enhanced food intake of diabetes mellitus (59), then the 'feeding centers' of the hypothalamus must differ from the rest of the brain in that they require insulin as muscle does for normal utilization of carbohydrate. Similarly, it is certain that most animals cannot eat when they are dehydrated, and also that after feeding there is a movement of fluid out of the rest of the body into the digestive tract (40, 55). But whether this movement can provide a signal that eating has taken place is not established, although it seems plausible. Again, food intake is responsive to changes in environmental temperature and to the circumstances of temperature regulation within the body (18); that the heat released during assimilation of food is a signal to the hypothalamus, however, is not accepted by all investigators. Finally, the maintenance of a constant depot of fat within the body takes place only under certain limited conditions of feeding and environment (45). In at least two species of animals the fat stores depend upon genetic strain and upon fat concentration in the diet (34, 61). One cannot state that any one of these possible 'signals' is not important; but it does appear that certain of them are more suitable for regulation than others. Shifts of water occur during digestion, for example, no matter what the composition of the diet, and there are also definite water requirements associated with regulation of body temperature and with activity, as well as with storage of protein and, to a lesser extent, of fat. Water might, therefore, provide a common denominator necessary for interrelationships in control of feeding, drinking, body temperature, activity, body size and energy intake (28). The extra heat of metabolism of food, the specific dynamic action (S.D.A.), offers similar advantages, in addition to being responsive to the metabolic state of the body in a fashion that could explain alterations in food intake following starvation and during growth, and when the composition of the diet is changed. High protein diets have a high S.D.A. and animals rarely become obese on such a diet, while high fat diets predispose to obesity in some animals and have a lower S.D.A. It is not necessary to inquire further into this

subject here, since it is the author's belief that a variety of factors is important and that it is not possible at the present time to assess quantitatively the relative significance of each.

SUPPLEMENTARY MECHANISMS

Presenting these generalized changes that could act upon the hypothalamus should not lead to a neglect of more definite, although possibly more limited, sensory mechanisms. The ability of the month, pharynx and upper esophagus to 'meter' both water and food is well established (1, 16, 17, 47, 52, 88), and so is the inhibiting effect of gastric distention (4, 47, 89). The sensation of hunger arising in the stomach, and of thirst referred to the mouth and pharynx, are powerful reminders of a need for food or water. Yet the disappearance of gastric hunger as fasting is prolonged, its absence during cold exposure (26), the normal feeding responses of animals without innervation of the gastrointestinal tract (41, 42) and the persistence of appetite after removal of most or all of the stomach (92), all indicate that either generalized or central perception is more critical than the localized one in achieving the overall regulation (13, 66). One may suppose, as Carlson did, that a newborn baby cries when its empty stomach contracts, that filling the stomach with milk inhibits the contractions and that this sets up a learned response where feeding is associated with relief of gastric pain (26). However, very young babies (just how young is uncertain) can be fed at intervals throughout the day with no periods of crying and no evident gastric distress (personal observation). They evidently experience a cycle of appetite-satiety-appetite, etc., without definite pain. Adult subjects sometimes report the same experience (60), as a well-known child psychiatrist assured this reviewer that gastric pains as an accompaniment of the hunger state were completely unknown to him.

The diagram of figure 1 presents a simplified outline of a multifactor concept of regulation of feeding, based on the conclusions that appetite is converted into satiety by the processes of eating and filling the stomach, by relief of hypoglycemia or inadequate supply of glucose, and by shifting of body water, as well as by the thermal stress of the S.D.A. This diagram may be incomplete since other reactions may remain now unknown. Its principal value is that it illustrates the ability of the central nervous system to take many different kinds of change within the

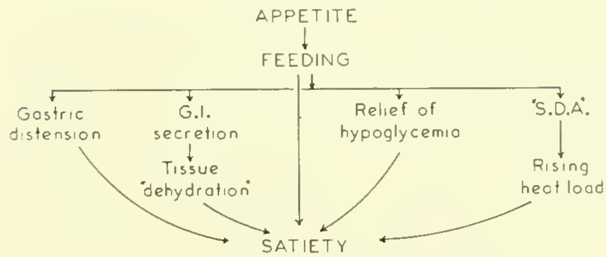

FIG. 1. Simplifieid outline of a multifactor concept of the regulation of feeding.

body and integrate them into a pattern of activity or response. Whether all of these factors act upon the hypothalamus is not known; but all of them must act eventually upon feeding reflexes, which means that they must either directly or through other neural pathways affect the motor nerve nuclei of the brain stem. One can understand how the three generalized changes—glucose lack, water movement and thermal gradients—might act upon the same neuron or upon all neurons. Wherever their critical actions, the end result of a deficiency of food must be active facilitation of reflexes necessary for feeding, as a lack of water in a similar fashion must facilitate drinking reflexes. The key reactions within the brain are facilitation and inhibition, applied discretely enough to allow animals to distinguish between need for food and for water and to provide a basis for specific hungers or appetites. That is, facilitation and inhibition must be selective. This implies a type of discrimination within the tegmentum or in mechanisms closely related to it and calls to mind Sherrington's conclusion that there is a spinal hunger state (77). He noted (p. 845), "As a broad rule, spinal reflexes are more easily elicited when a well-nourished animal is hungry and expecting food, and less easily when it has just heavily fed. There is, so to say, a spinal hunger."

THIRST

In writing about thirst[4], authors seem inclined to follow the pattern already outlined for hunger and appetite. Andersson (9), Andersson & McCann (10, 11) and Greer (39) have all observed drinking to follow perfusion or stimulation of the hypothalamus.

[4] Wolf has recently published a monograph on thirst that is both informative and interesting, and has immediately become the classic discussion of this subject (93).

In the goats studied in Andersson's laboratory, drinking was accompanied by antidiuresis which combined to give the animal a phenomenal excess of water within the body (9, 10). Their results suggest the localization of a thirst mechanism in the rostrodorsomedial portion of the hypothalamus. Destruction of this region reduced or abolished drinking in dogs (11). A more precise type of localization has been reported by Stevenson *et al.* (81) and Montemurro & Stevenson (64, 65) who find that discrete bilateral lesions in the lateral hypothalamic area reduce or even abolish drinking in rats. They regard this as a drinking 'center' analogous to the lateral feeding mechanisms described by Anand (6). A general confirmation of their results was published by Morrison & Mayer (67), with certain differences, including lesions of a larger size than those of Montemurro. A report by Gilbert suggests a location outside the hypothalamus for the thirst mechanism, but further study is needed since he has reported that lesions of the subcommissural organ and the injection of extracts of this organ both have the same effect in reducing drinking, where one would suppose on theoretical grounds that the two procedures should give opposite results (36).

A state of persistent drinking, analogous to hyperphagia and independent of diabetes insipidus, does not appear to have been discovered. If there are inhibitory mechanisms for drinking, either they are not localized well enough to be destroyed by experimental lesions or else the lesions thus far created are not in the critical regions. If the brain does, indeed, contain osmoreceptors, one can imagine how they might at one time inhibit urine production, induce drinking and limit food intake because the body is relatively low on water. At another time they could allow urine to flow without inhibition, prevent drinking and facilitate feeding reflexes when bodily reservoirs of water are relatively full and food is lacking (37). The interaction of neurons responding to availability of water with those sensitive to conditions of temperature regulation might offer the beginning of simple discriminations which could be refined and made more specific by sensory input from other parts of the body, including taste, distance receptors and the innervation of the digestive tract. In other words, the permutations and combinations possible among only a half dozen different reactions and mechanisms known to be related to feeding and drinking may well include most of the conditions under which both food and water intake are known to respond to changes in the animal and its environment. Experimental data suggest both such an interrelationship (67, 82), and also a certain degree of independence of the appetite and thirst mechanisms (65, 67).

LOCOMOTOR ACTIVITY

Integration of feeding and drinking with regulation of other factors in energy exchange was noted above. In conclusion, activity should be mentioned also as one of the mechanisms assisting with water and food intake. Laboratory animals with food either present or supplied at intervals may have little need for foraging. This, of course, is an artificial situation, for under natural conditions the higher animals all move about in the process of getting their day's rations. Activity precedes eating (90), while partial starvation increases spontaneous activity (80, 91). The observations that either an increase (57) or a decrease (43) in activity may follow appropriate lesions of the hypothalamus, therefore, seem to complete the chain of reactions in which the body correlates the variables of energy exchange and at the same time utilizes each of the several variables to facilitate the regulation of the others. For this purpose, at least, a regulation can be defined as the end result of the integrative actions of the nervous system in the control of a physiological variable—in particular, a variable exchanged between the organism and its environment.

SUMMARY

Progress in this field within the past 15 years has led to the following conclusions and hypotheses.

a) Water and energy exchange can be measured under conditions where reliability and accuracy are possible, and where the regulation of these variables by the body can be studied.

b) Lesions in the hypothalamus may alter the regulation of water excretion, water intake, food intake, body temperature, spontaneous activity or body weight.

c) Stimulation of the hypothalamus or perfusion with certain solutions will activate at least some of the mechanisms which have been identified in animals with experimental lesions.

d) These observations suggest the hypothesis that the hypothalamus is an integrator of regulations concerned with water and with energy exchange.

e) The integration is affected by sensory input into the brain from the organs of special sensation and

from the skin, as well as from receptors in the mouth, pharynx and gastrointestinal tract, but it is based upon more generalized types of change in the internal environment. These generalized changes are believed to influence the neurons in a manner which leads to selective facilitation or inhibition of reflex patterns essential to eating and drinking.

f) The generalized changes include the availability of water and of glucose and other metabolites, and the conditions of temperature regulation. Other important variables of this type may be as yet unknown.

g) Gastric hunger and pharyngeal thirst remain as important problems in general sensation. Under natural conditions they have a part in motivating feeding and drinking, but they are not required for the regulation of either energy or water exchange.

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CHAPTER XLVIII

Central control of the bladder[1]

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CHAPTER CONTENTS

THE NEURAL CONTROL of the urinary bladder is a matter of considerable clinical importance to neurologists and to urologists. To the physiologist, the urinary bladder presents unique but little exploited opportunities for study. It is the most accessible smooth muscle of the body and can be studied quantitatively *in vivo* with relatively little interference with it or with the body as a whole. Also, the bladder is relatively independent of other visceral organs, so that its control by the brain can be studied without the complexities presented by, for example, the cardiovascular system.

Although neurologists, urologists and physiologists have a community of interest in the bladder, they have little community of thought. The clinical disciplines have developed a fairly uniform view, apparently little influenced by physiological experiments on animals although there is a substantial similarity in methodology which should make translation from animals to man easy. A further paradox is that physiological thinking on the subject has been more influenced by classic neurological concepts, especially those of Hughlings Jackson, and by the now classic experiments of a urologist, F. J. F. Barrington. This chapter will bring the neurophysiological and clinical data into juxtaposition.

METHODS OF STUDY

Simple Pressure Recording

The bladder containing an arbitrarily determined volume of a fluid is connected to a manometer or a tambour by means of a urethral catheter. The bladder contracts under varying degrees of isometricity, depending on the size of the connecting tube, the density of the fluid or the stiffness of the tambour membrane; the limiting case is a strain gauge or a

[1] Based in part on studies aided by grants from the Washington State Research Fund for Biology and Medicine and by a contract (N113-150) between the Office of Naval Research, Department of the Navy, and the University of Washington.

similar device which requires only an infinitesimal movement of fluid from the bladder. The recording being isometric, the activity of the bladder is manifested as pressure whereas, in other devices, the volume of the bladder actually decreases in varying degrees and the contraction is manifested in the movement of fluid as well as in pressure. The muscle progressively contracts at a shorter length of fiber, a condition which in skeletal muscle decreases the tension produced. No thoroughgoing comparisons of isometric and isotonic recording of bladder contraction have been published.

Cystometry

The variety of cystometers is bewildering. All 'short-circuit' the sphincters by the urethral catheter so that only detrusor activity is studied. This situation has analytical value but dictates caution in reasoning from cystometrograms to normal micturition. All cystometrograms relate intravesical volume to pressure, the latter by convenience and convention being graphed on the ordinates. In some critical details, cystometers vary considerably. Most are isotonic but some are isometric. Second, in some, the fluid flows into the bladder continuously; in others by equal sudden increments, spaced equally in time. However, provided certain strictures on the two methods are observed, there is no demonstrated significant difference in the resulting pressure-volume curve.

A continuous flow should be delivered at a pressure which results in equal increments per unit time and requires volume monitoring. This method is defended as more natural although, at best, the flow exceeds the rate of urine formation. The resistance of the catheter orifice is a major factor unless the filling is exceedingly slow, in which case deterioration of an animal preparation, limitation of the number of determinations and time consumption enter the picture. A double-lumen catheter is necessary for recording true intravesical pressure, and this necessity aggravates the problem of catheterizing small animals such as the cat.

In the discontinuous increment method, the instantaneous rate of fluid input is higher, and the record is more influenced by *a*) the viscous properties of the bladder wall and *b*) errors related to the recording of pressures during fluid movement. The position of the manometer is irrelevant. The abrupt rise of recorded pressure with each increment is an orifice-viscosity factor and should be regarded as a convenient signal, marking the time of the increment. A double-lumen catheter eliminates the orifice factor but is not needed if the intravesical pressure is read at the end of the interval between increments when the pressure curve is asymptotic and no fluid is flowing.

The cystometer yields, in addition to the pressure-volume curve, a measure of the micturition threshold, i.e. the volume (or pressure) which precipitates the vigorous, sustained, easily recognizable, micturition contraction of the detrusor. If the record is isometric, or to a lesser extent, if it is semi-isotonic, the rate, strength and duration of detrusor activity are also measured. Both the threshold volume and the micturition-reflex record are measures of the excitability of the reflex arc, a state which is determined by facilitation and inhibition from the brain.

Micturition Threshold Determinations in Intact Animal

The volume of a 'spontaneous' micturition (i.e. that occurring when the bladder of an unanesthetized uncatheterized animal is filled by urine secretion) is, by definition, a measure of the micturition threshold, subject to correction by the amount of residual urine (36). Unlike cystometry, 'spontaneous' micturition volume determinations assay the functioning of the whole urinary tract and the sum of the neural influences from supraspinal levels, acting on the sphincters as well as on the detrusor. The method is comparable to the 'times and volume' observation of a clinical patient. The technique involves an efficient metabolism cage pan connected with a volume recorder. Induction of diuresis permits more micturition volumes to be measured in a unit time.

Other Methods

Electrodes may be applied to the bladder wall or to the afferent or efferent neurons innervating the bladder. Fluoroscopic, roentgenographic and cinefluorographic techniques have also have been used, and various arrangements of pressure recorders have been utilized to observe sphincter activity separately or simultaneously with detrusor activity.

CENTRAL CONTROL OF BLADDER TONUS

Few words are as loosely defined and have so many vague connotations as 'tone' or 'tonus.' It seems best to use these words in a generic sense to mean a kind

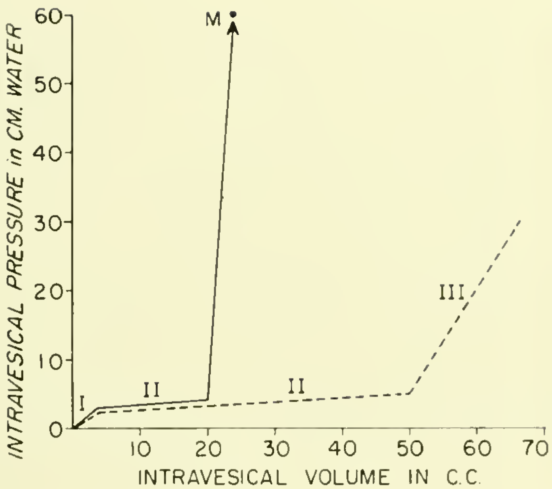

FIG. 1. Schematic cystometrograms. *M* indicates peak pressure during micturition contraction. *Segment I*, or the initial rise, is segment from zero to first point of inflection. *Segment II*, or the tonus limb, begins at the first inflection point and either ends at micturition contraction or, in the absence of micturition reflex, continues into *Segment III*, the ascending limb. [From Tang & Ruch (32).]

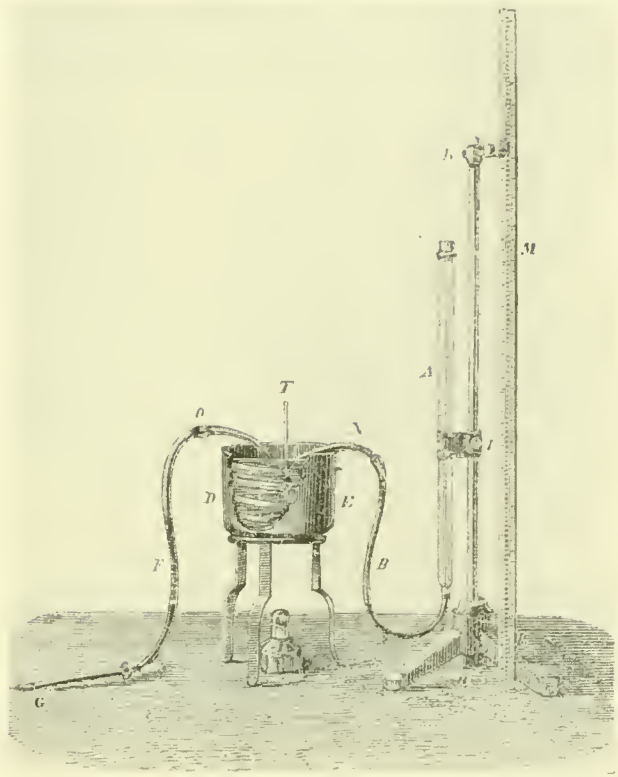

FIG. 2. Cystometer used by Mosso and Pellacani who were the first to record cystometrograms. [From Mosso & Pellacani (22).]

or class of things, and to modify them by specific terms to denote more restricted meanings, e.g. 'active,' 'neurogenic.' (Thus may be avoided the nomenclatural impasse reached by physiologists in respect to 'inhibition.') Also, in an area in which quasivitalistic thinking has occurred, it seems best to use an operational definition. Thus, 'tonus' of the bladder is defined simply by the pressure-volume curve yielded by a cystometer.

Cystometrogram

Figure 1 shows a diagrammatic cystometrogram and introduces a terminology, which is without prejudice in respect to cause, for the various phases of the record. Although the zero pressure on the manometer is set at the level of the symphysis pubis, most cystometrograms show a definite rise in intravesical pressure with the first increment of volume (Segment I). The reason for this has not been explicitly stated. After a definite inflection, the $\Delta P/\Delta V$ rises slowly, usually along a slightly positively accelerated curve—Segment II, or the 'tonus limb.' Normally, this limb is truncated by the occurrence of micturition, indicated by the arrow labelled M, the maximum pressure developed (semi-isotonic) being indicated by the dot. If micturition does not occur, Segment II continues, the curve 'accelerating' more rapidly until it climbs quite steeply. The quasi-inflection, although often sharp, is greatly exaggerated in the diagram. This ascending limb is designated Segment III to provide for the possibility that an additional component of the bladder wall is involved. It is noteworthy that micturition usually occurs before or at this point of inflection, if it occurs at all.

Mosso & Pellacani (22), who first determined the pressure-volume curve of the bladder using the cystometer shown in figure 2, and those who have followed them have been preoccupied with the flatness of Segment II and have endowed the bladder with a property of 'adaptation'; or 'accommodation.'[2] Several authors (8, 9, 19), perhaps following Sherrington, have likened the bladder's reaction to

[2] These terms are unfortunate because they hint at an active tonic detrusor process, and both have other technical meanings in neurophysiology. In a recent clinical work, Segment II is attributed to a stretch reflex, although a stretch reflex, did it exist, would cause the pressure to rise, the reverse of accommodation.

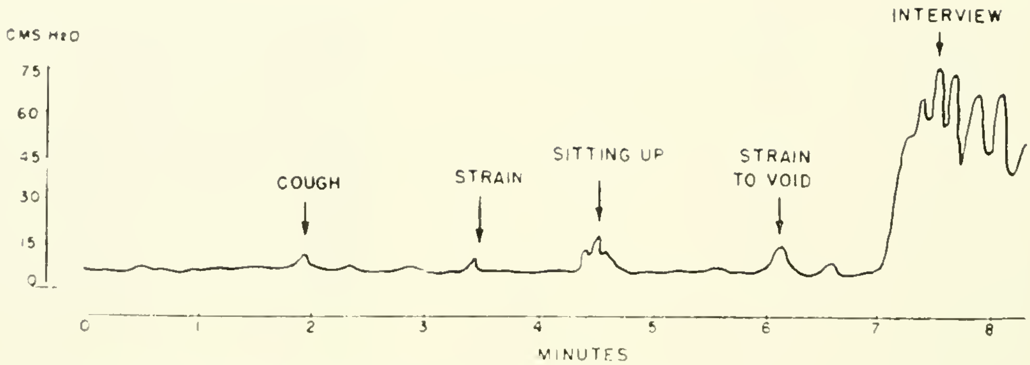

FIG. 3. Tambour tracings of intravesical pressure obtained from a patient showing effects of increased intra-abdominal pressure and of emotional stimuli resulting from a psychiatric interview. [From Straub *et al.* (29).]

the stretch imposed by filling to the postural reflexes of skeletal muscle. The tonus limb is thought by some (8, 9) to represent an interplay between an excitatory reflex (tonus) and an inhibitory reflex (adaptation or accommodation), comparable broadly to the shortening and lengthening reaction of extensor muscles. According to this analogy, the degree of bladder tonus is neurally determined. Denny-Brown & Robertson attributed the basic neural mechanism of tonus to the plexus of neurons lying on the bladder wall whereas Langworthy's concept was a neural mechanism analogous to that controlling the myotatic reflex of skeletal muscle, a spinal reflex controlled by the brain stem. Clinical workers, with the exception of Nesbit and his co-authors (26, 27), either have made no interpretation or have accepted the neurogenic origin of bladder tonus explicitly or implicitly.

Absence of Higher Control of Bladder Tone

In figures 4 and 14 to 16 is presented a series of experiments in which cystometrograms were obtained from intact unanesthetized cats and from the same or other cats after segmental transections at various levels of the neural axis, the determinations being made after the effects of ether anesthesia had dissipated. It will be observed from the take-off point of the arrows denoting micturition that the various transections profoundly altered the micturition-reflex threshold and hence the excitability of the micturition reflex. Transections at some levels increased micturition-reflex excitability over the pre-existing state; at other levels, transection decreased the threshold. In the whole series of experiments, the thresholds ranged from 4 ml (intercollicular decerebration) through 66 ml for the intact cat to complete failure of the reflex in acute spinal preparations. These threshold changes will be correlated with levels of transection in a later section.

The point at issue here is the comparison within each diagram (representing a single animal) of Segment II up to the point of micturition. For each animal, the tonus limb is identical, within the limits of experimental error, in the normal state and after each of the sequential transections used in the particular experiment. Although transections at various levels between a hypothalamic level and the spinal cord[3] varied the micturition threshold from a few milliliters to complete failure of micturition, the operations had no effect on bladder tonus. It is concluded therefore that bladder tonus, unlike the micturition reflex, is not subject to either facilitation or inhibition from supraspinal levels. If bladder tonus is a reflex, it is unique among reflexes in not being subject to higher control.

The literature contains many reports of changes in intravesical pressure following stimulation of various brain-stem and cortical structures, and such changes have usually been identified with tonus. An alternative explanation is that they are fractional manifestations of the micturition reflex, elicited by a fractional activation of the complex neural apparatus controlling the excitability of this reflex. Striking changes of intravesical pressure (fig. 3) have also been induced in man by stimuli with emotional significance (29). Whether these are tonus changes or

[3] Langley & Whiteside (18) made a similar observation after spinal transection in the dog.

abortive micturition contractions is the question. However, it is fair to point out that all possibility of descending influences on bladder tonus are not ruled out by the animal experiments since the highest transections deprived the animals of much of their perceptual and emotional apparatus. The intact unanesthetized animals were kept in a tranquil state, a requisite for obtaining a cystometrogram.

Vesicle tonus is not a spinal or ganglionic reflex. This fact has been demonstrated by Carpenter & Root (5) and by Tang & Ruch (32) in experiments in which any tonic mechanism depending on spinal reflex arcs or postganglionic 'reflex' arcs, served by the intramural plexus of the bladder wall, was negated by acute spinal transection, sacral rhizotomy, ganglionic blockade, ether and pentobarbital anesthesia, or anoxia (death). No change in the tonus limb to the point of micturition was caused by acute spinal transection (fig. 4), procainization or section of the sacral roots (fig. 5), or by deep anesthesia or death (fig. 6). Carpenter & Root (5) also found no difference in the tonus limbs of cystometrograms for normal lightly-anesthetized cats and those treated with tetraethylammonium bromide (TEA) which negates both the sympathetic and the parasympathetic innervation and, presumably, mural ganglionic transmission. Nesbit & Lapides (26) and Langley & Whiteside (18) reported experiments of the same

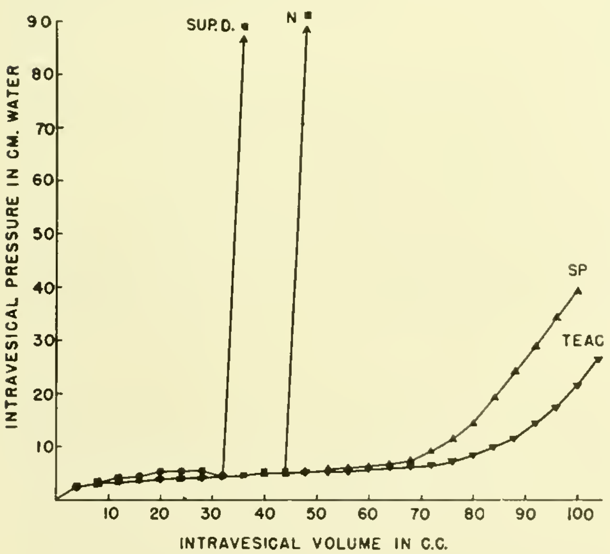

FIG. 4. Cystometrograms comparing Segment II of the normal (*N*) and acute spinal preparation (*SP*). For significance of the *SUP.D* and *TEAC* curve, see the text. [From Tang & Ruch (32).]

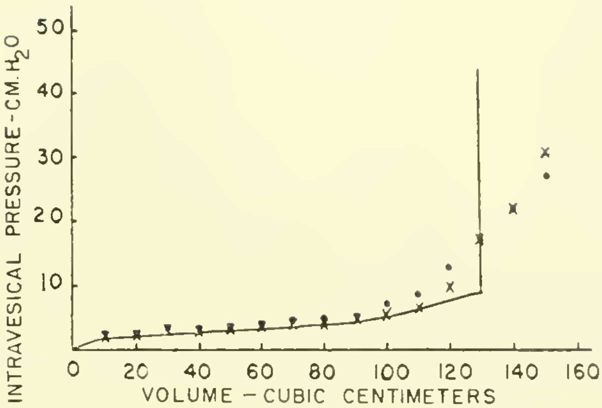

FIG. 5. Cystometrogram of a cat anesthetized lightly with pentobarbital (—) and after procainization (×) or section (·) of sacral roots. [From Carpenter & Root (5).]

weight, performed on dogs. The hypertonia after pelvic nerve section, described by Langley & Whiteside, is ascribable to exposure of the bladder.

Cystometrogram and Physical State of Bladder Wall

In many experiments (figs. 14 to 16), identical tonus limbs were obtained in repeated determinations. In another set of experiments (figs. 4, 7 and 8), when the micturition reflex was in abeyance through spinal transection, repeated cystometrograms caused the cystometric curve, especially its third segment, to shift to the right after each determination. The only significant difference[4] in the two sets of experiments was the presence or absence of the micturition reflex. In its absence, an initial single filling of the bladder, at moderate pressures, altered the tonus limb of the cystometrogram. It follows, then, that the cystometrogram, rather than reflecting the neurogenic tonus, reflects the physical condition of the bladder wall.

If tonus and accommodation or adaptation are not neurogenic, their intimate nature falls outside the scope of this chapter but may be briefly indicated by the following summary of Remington & Alexander's (28) recent study. The bladder wall exhibits a mixture of viscous and elastic properties

[4] In some cases, as in figs. 4 and 7A, a neurectomy or a drug was interposed and, at first, the shift in the tonus limb was ascribed to these variables. However, the same shift occurs when the cystometrogram is simply repeated, as in fig. 8. The same phenomenon can be seen in the records of others before and after introduction of a variable but seems to have escaped notice.

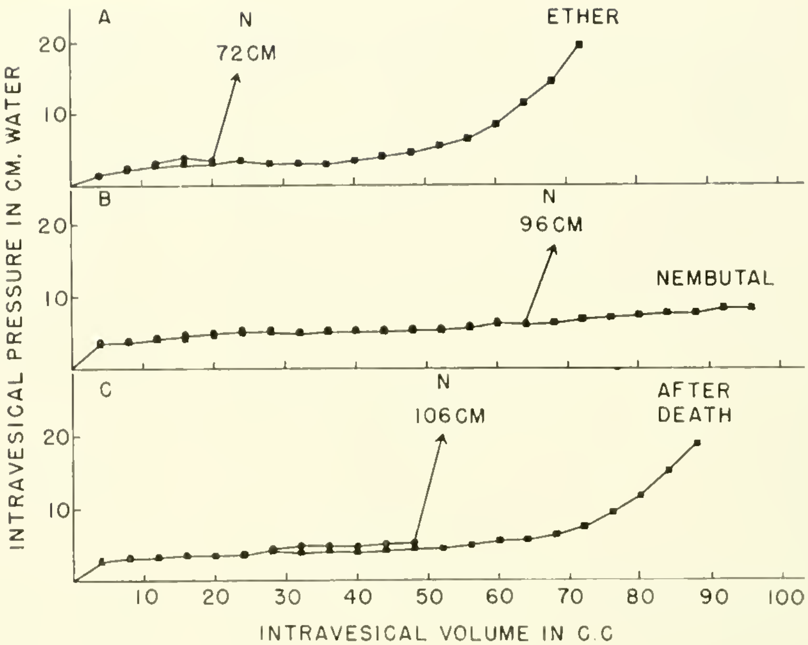

FIG. 6. Graph showing *A*, cystometrogram in intact state (*N*) and that under ether anesthesia; *B*, cystometrogram in intact state and that under pentobarbital anesthesia, *C*, cystometrogram in intact state and that after death. [From Tang & Ruch (32).

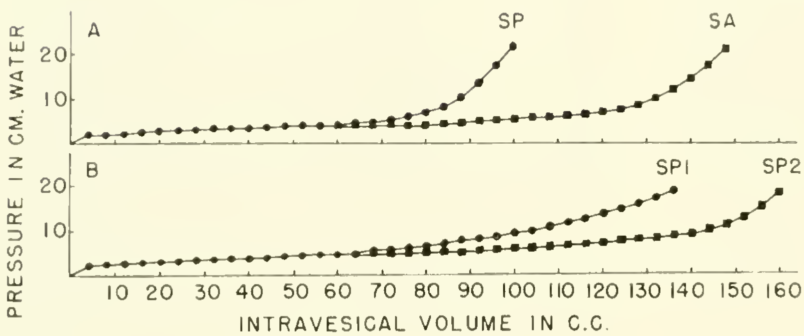

FIG. 7. *A*. Cystometrograms following spinal transection (*SP*) and subsequent sacral rhizotomy (*SA*). *B*. Spinal cystometrograms showing shift of second curve (SP_2) to right of the first (SP_1). [From Tang & Ruch (32).

similar to those of skeletal muscle. The viscous properties explain the resistance to sudden stretch, the subsidence of this resistance and a hysteresis effect. On release of stretch, the pressure curve fails to retrace the curve followed on the application of stretch. The failure of two similar applications of stretch, as in figure 8, to yield the same curve is a similar phenomenon.

A physical change in the bladder wall which shifts the cystometric curve to the left (hypertonicity) has also been produced experimentally. According to Carpenter & Root's analysis (5), this hypertonicity (fig. 9) occurs after section of the pelvic nerve or, to a lesser degree, of the sacral roots; develops a few days postoperatively; is not due to infection; and is accompanied by a hypertrophy of the bladder wall (4), manifested in weight and histological appearance. The degree of hypertrophy was related to the amount of residual urine and the intravesical pressure; these were greater after pelvic nerve section which leaves intact the tonic innervation of the external sphincter via the pudendal nerves.

Another and more striking way in which the physical status of the bladder can be altered in the direction of 'hypertonicity' was shown quantitatively by Veenema *et al.* (34). They exteriorized the ureters of dogs, preventing the bladder from receiving its normal periodic filling and emptying. The cystometrogram taken 39 days postoperatively showed a sharply ascending Segment II (fig. 10). Unfortunately, the behavior of the bladder in repeated cystometrograms was not studied. This and the time course of recovery from hypotonicity induced by stretch clearly deserve

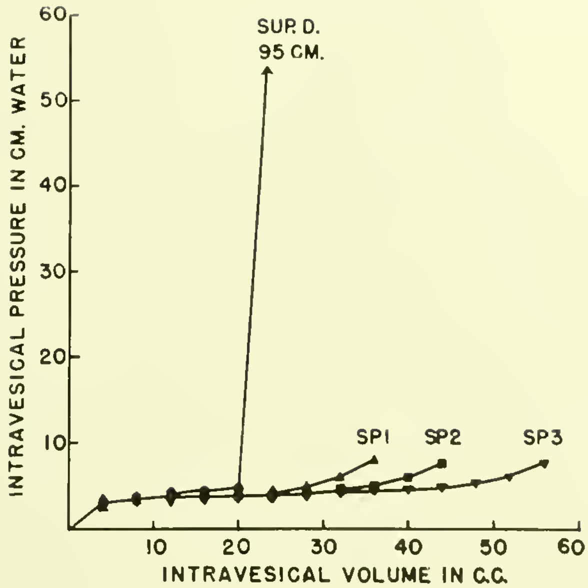

FIG. 8. Graph showing cystometrogram following supracollicular decerebration (*SUP.D*) and three successive cystometrograms obtained at moderate pressures following spinal transection (*SP*$_1$, *SP*$_2$, *SP*$_3$). [From Tang & Ruch (32).

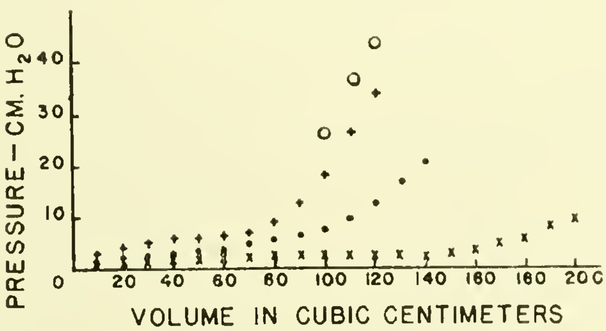

FIG. 9. Bladder volume-pressure curves of cats anesthetized with pentobarbital 13 days (×), 27 days (·) and 73 days (+) after bilateral pelvic nerve section. *Circles* show the magnitude of autonomous contraction 73 days after the operation. [From Carpenter & Root (5).]

examination which should aid in the interpretation of human neurogenic bladder dysfunction.

Summary

Experimental analysis shows that neural transections which strongly affect the excitability of the micturition reflex arc are without effect on bladder tone. Other conditions which would interrupt any postulated parasympathetic or spinal reflex arc or a

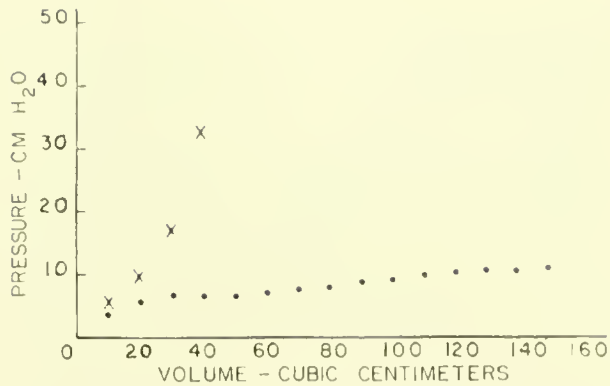

FIG. 10. Cystometrograms from a dog with micturition prevented by general anesthesia and sacral root block (·). *Crosses* show the pressure-volume relation 39 days after both ureters were transplanted to exterior of the body. [From Veenema *et al.* (34).]

mural ganglionic 'reflex' subserving tonus are equally without effect on detrusor tonus. On the other hand, the three procedures which do depress or elevate the tonus limb of the cystometrogram, namely, repeated cystometric determinations when the micturition reflex is in abeyance, chronic pelvic nerve section and chronic prevention of bladder filling, affect the physical state of the vesicle wall. It is therefore concluded that bladder tonus is not neurogenic but reflects the physical state of the bladder wall, and that tonus changes appearing to be neurogenic are mainly secondary to neurogenic alterations in the micturition reflex which is the guardian of the physical state of the bladder wall. This conclusion has implications for cystometric diagnosis and the interpretation and handling of human neurogenic bladder dysfunction.

Pathophysiology of Bladder Tonus in Man

In man, as in the cat, there is experimental and presumptive evidence that the slight hypertonia from acute neural insults and the more impressive hypertonia from chronic insults are not based on a putative reflex vesical tonus mechanism.

Using spinal anesthesia and TEA, Nesbit and his co-workers (26, 27) have examined human cases of acute and chronic spinal transection and a variety of cases of other neurogenic bladder dysfunctions, and the results agree entirely with the animal experiments cited above. Therefore it can be concluded that hypotonia in man reflects, not the state of a tonic reflex, but the promptness of catheterization

and the thoroughness of the procedures such as tidal drainage designed to prevent distention or shrinkage of the bladder.

Extreme hypertonicity (climbing tonus curve) occurs as an intermediate or late stage after spinal transection and, according to some, as the final state after interruption of the sacral reflex arc (fig. 11). The steeply rising tonus limb is interrupted by frequent, but feeble, brief contractions. In spinal transection cases, tonus becomes more normal when the micturition reflex becomes more normal.

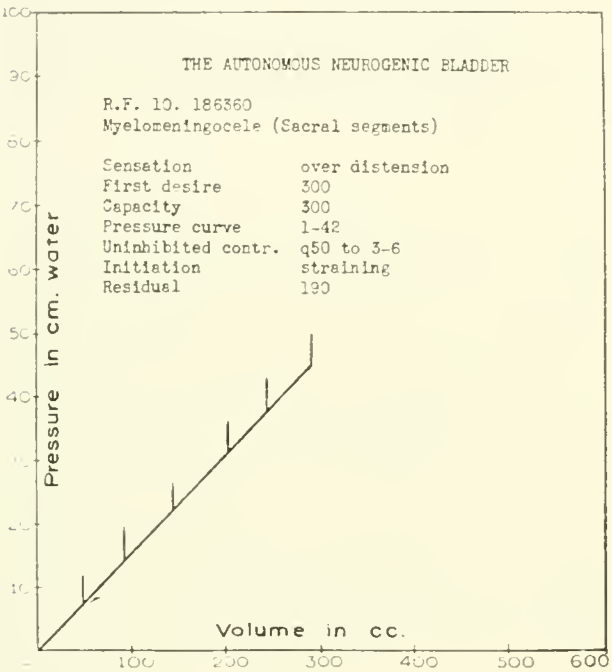

FIG. 11. Autonomous neurogenic bladder dysfunction from sacral root damage. Note the frequent small contractions superimposed on steeply ascending tonus limb. [From McLellan (20).]

In man, marked hypertonia has not been analyzed as thoroughly as atonia. However, figure 12 shows that a moderate degree of hypertonia (20 cm of H_2O) changed after administration of TEA only by a slight shift to the right, probably the result of a previous cystometric determination. There is therefore no evidence that hypertonia is neural in origin. Unfortunately, the behavior of experimental or clinical hypertonia has not been studied by repeated cystometrograms. Figure 12 suggests that repeated filling in the absence of micturition decreases the tonus. Although the mechanism is less certain, the association of small frequent micturitions with hypertonia suggests that it is a physical change secondary to the altered micturition reflex. Similar ascending tonus curves are seen experimentally in two circumstances, *a*) after chronic decentralization of the bladder by pelvic nerve section, when frequent abortive muscular contractions are acting against the resistance of the internal sphincter, and *b*) when the ureters are exteriorized (5, 34).

HIGHER CONTROL OF MICTURITION

The prevailing clinical view of the micturition reflex in man has been developed and sustained with little regard for the results of laboratory experiments. The immediate agent in micturition is a spinal reflex employing the sacral segments. Clinicians consider the cerebral control to be purely inhibitory and think of micturition itself as an unleashing, or disinhibition, of the spinal reflex. Altogether, clinical thought on bladder dysfunction after spinal cord lesions has undergone a remarkable evolution. Prior to World War I, Bastian's law ('complete areflexia is a criterion of complete spinal transection') included the bladder. Between the two wars, automatic

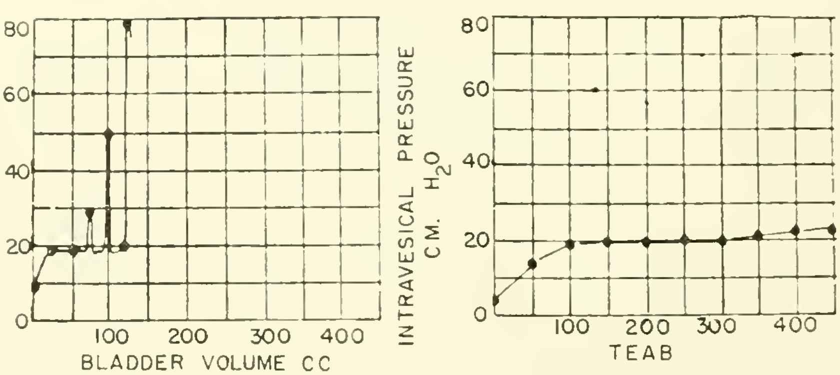

FIG. 12. *Left.* Diagram showing an elevated Segment II of an 'uninhibited neurogenic bladder' in man. *Right.* After tetraethylammonium bromide, the micturition contractions disappear but the hypertonus persists. [From Nesbit & Lapides (26).]

bladders were observed and encouraged by careful nursing. Since World War II, the orientation, including surgical intervention, has been toward controlling overactivity of the bladder.

The neurophysiologist draws an analogy between the myotatic reflex of skeletal muscle and the micturition contraction, both being reflexes in response to stretch and both being relatively sustained activities. He thinks of such reflexes in higher animals as depending not on a simple reflex arc but on such an arc played upon by facilitation and inhibition from several levels of the brain stem. A moment's reflection suffices to show that a reflex arc inhibited from the cerebral cortex is not a typical pattern for either visceral or somatic mechanisms, nor does this oversimplified concept afford any explanation of the period, lasting days, during which the spinal reflexes are depressed. Physiologically, posttransection areflexia or hyporeflexia (spinal shock) are ascribed to the blocking of descending facilitatory impulses, missing from the urologists' schemata. Recent physiological investigations seem to indicate that the higher control of the micturition reflex and the myotatic reflexes of antigravity muscles can, *mutatus mutandis*, fit into the same framework.

Levels of Bladder Control

The following account is based upon and extends the classic, but neglected, observation of Barrington (1, 2) which proves that the upper pons contains a powerful micturition facilitatory area. Some of the same observations were also made by Langworthy and his co-workers (19). However, for the sake of simplicity of presentation, and because their experiments involved anesthesia and their interpretations were different, the following account is based upon a single set of experiments (31, 33). The levels of transection referred to in the text are shown in figure 13. Description will be in terms of the most rostral level maintaining continuity with the final common path rather than the transection yielding the preparation.

ANTERIOR PONTINE PREPARATION. When the spinal cord of the cat is divided, no amount of fluid introduced into the bladder will elicit even the slightest micturition contraction. Complete vesicle areflexia exists. However, when the brain stem is transected just above the pons or at the classic intercollicular level, quite the opposite happens; not only does the micturition reflex occur, but the threshold volume is only a fraction of the normal and the detrusor contraction is powerful and sustained (fig. 14). If a second transection is made a few millimeters caudally (fig. 15), if the anterior pontine tissue is cooled (East, N. R., J. J. Milford & T. C. Ruch, unpublished observations) or if the appropriate pontine locus[5] is focally destroyed, the micturition reflex is no longer elicitable—the preparation is virtually a spinal animal in respect to micturition. Thus, as Barrington rightly concluded, the anterior pons gives origin to a descending tract which facilitates the spinal micturition reflex arc. When this descending pathway is the only remaining suprasegmental influence, the micturition reflex is so facilitated that the threshold volume is but a fraction (typically one-sixth) of that required to trigger the reflex in the intact cat. From these experiments it may also be concluded that the neural structures rostral to the anterior pons exert a net, powerful, inhibitory action on this reflex.

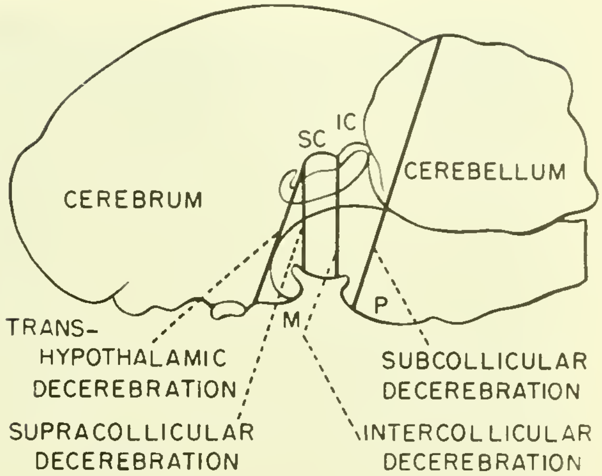

FIG. 13. Schematic representation of levels of brain-stem transection. *SC*, superior colliculus; *IC*, inferior colliculus; *M*, mammillary body; *P*, pons. [From Tang (31).]

Although the level of control is slightly more rostral for the bladder, there is a basic similarity to the tonic brain-stem influences on other visceral structures (e.g. blood vessels) and on the postural reflexes of the antigravity muscles (decerebrate rigidity).

ROSTRAL MIDBRAIN PREPARATION. If a supracollicular transection is performed a few millimeters higher, along the line so labelled in figure 13, an inhibitory

[5] Bilateral focal lesions in the dorsal tegmentum at the isthmus level, immediately ventral to the lateral angles of the periventricular gray matter, destroy the pontine center (33).

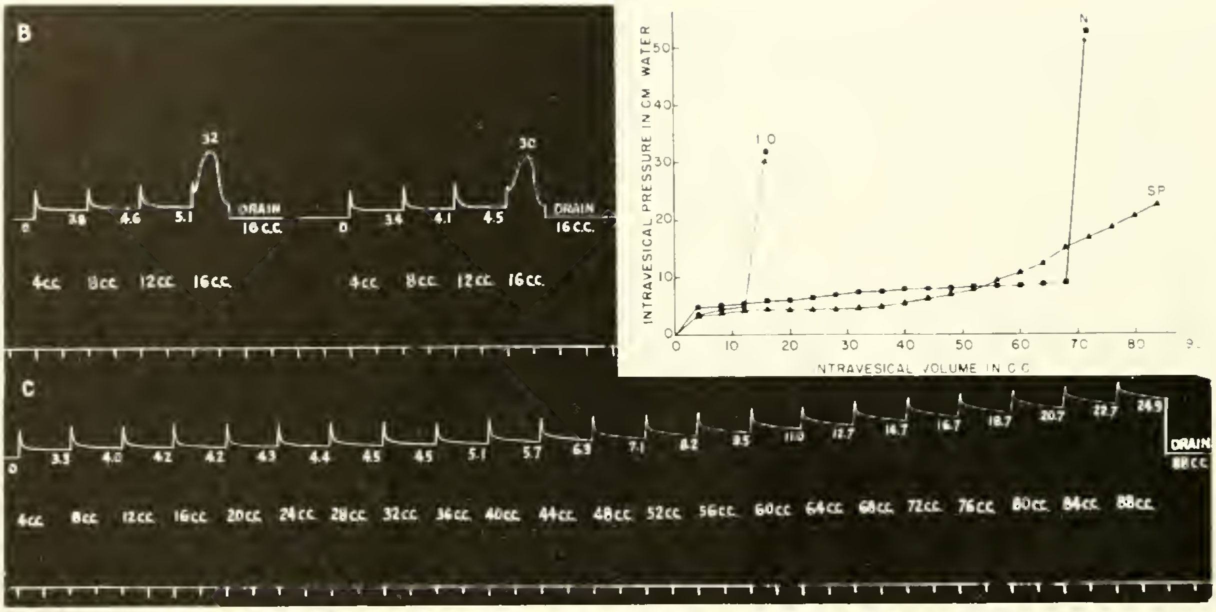

FIG. 14. Tambour records of cystometric determination with manometric notations. *B*. Two successive records after intercollicular decerebration. *C*. After spinal transection The reconstructed cystometrogram also shows a control normal curve. In this and subsequent cystometrograms the following abbreviations are used.

SUB.C., subcollicular transection | *SUP.D., supracollicular decerebration*
I.D., intercollicular decerebration | *T.D., transhypothalamic decerebration*

[From Tang & Ruch (32).]

component is identified. Although the threshold volume needed to elicit micturition is smaller than normal (fig. 4), it is sometimes only slightly smaller and is always considerably larger than the small volumes sufficing in the intercollicular decerebrate preparation. Converting a rostral midbrain preparation into an anterior pontine preparation by performing an intercollicular transection results in a pronounced lowering of the threshold (fig. 16, right). Thus, the pontine facilitatory area is partially balanced by a midbrain inhibitory area.[6] One can visualize two descending streams of impulses, one increasing and one decreasing the excitability of the preganglionic neurons supplying the bladder, the two summing algebraically. The midbrain area may, of course, be inhibiting the pontine area rather than or as well as the final common pathway. Both areas must receive an afferent input from below since both act when the brain rostral to each has been ablated.

[6] Focal lesions (33) have localized this area bilaterally in the tegmentum, just lateral to the central gray matter, at the caudal superior collicular level.

POSTERIOR HYPOTHALAMIC PREPARATION. An initial transection slightly rostral to the superior collicular level (transhypothalamic decerebration) yields a very low micturition threshold, averaging 8 ml in seven experiments. A subsequent supracollicular transection elevates the micturition threshold dramatically (fig. 16, right), the average now being 29 ml as would be predicted. The threshold change for six of the seven animals was an increase of threefold or more. Thus, again, two conclusions can be drawn: *a*) that the wedge-shaped block of tissue between the two levels of decerebration contains a powerful facilitatory area[7] and *b*) that the net effect of the tissue rostral to the transhypothalamic area is strongly inhibitory to the micturition reflex. The marked reduction in threshold to 4 to 12 ml documents a powerful, rostral, net inhibitory effect, presumably from the cerebral cortex and the rostral hypothalamus, although this point was not specifically examined.

[7] Localizing experiments placed the effective locus in the mammillary region (33).

STIMULATION EXPERIMENTS. It is by no means certain that all of the central influences on the micturition reflex are revealed by transection experiments which disclose only those which are tonically (continuously) active. From stimulation experiments, there is strong likelihood that the paracentral lobule, the premotor area, the posterior cingulate gyrus (15), the posterior pyriform cortex and amygdala (13), and even the cerebellum (6) are concerned in vesicle control. In fact, almost every cerebral and brain-stem structure has been implicated by one author or another. It is significant, in view of the inhibitory role assigned to the cerebral cortex, that strong micturition contractions are readily produced from cortical stimulation. Stimulation experiments designed to test the relationship of the various cortical areas to the micturition reflex are yet to be carried out. Such experiments are usually interpreted in terms of tonus. To explore inhibitory functions an excitatory background is required, and the micturition reflex, but not tonus, provides this.

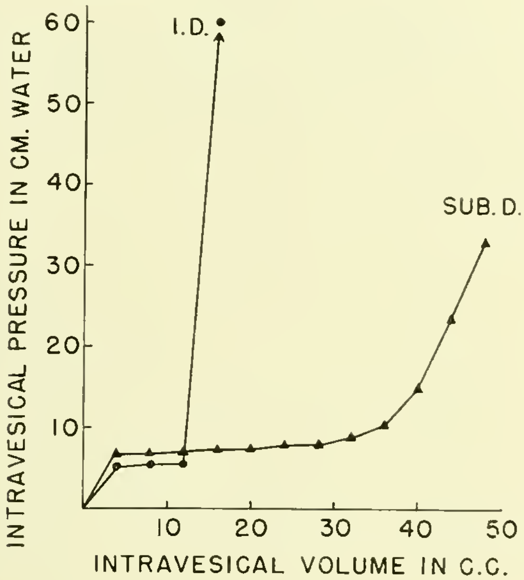

FIG. 15. Cystometrograms showing change in micturition reflex when an anterior pontine preparation (*ID*) is transected a few millimeters caudally (*SUB.D*). [From Tang & Ruch (32).]

Detailed correlation of brain-stem lesions and stimulation experiments (14) will not be attempted since the latter do not reveal areas inhibitory to the micturition reflex, since the significance of the response is not clear and it is uncertain whether or not descending fibers from a higher level are being stimulated. The last has been well shown by Grossman & Wang (11). Stimulation of the general region of the septum pellucidum and the medial preoptic area produced micturition-like contraction. When this area was chronically destroyed, the bladder responses to stimulation of the hypothalamus caudal to the lesion, except the region of the Barrington facilitatory area, became much smaller and more poorly sustained. Whether the septal-preoptic area

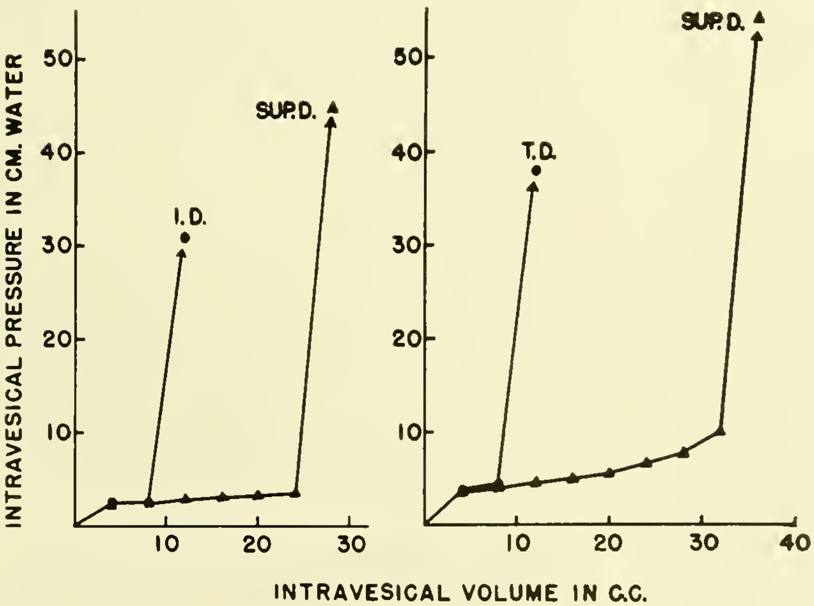

FIG. 16. Cystometrograms showing that the micturition threshold is higher after supracollicular decerebration than after intercollicular transection (*left*) or after transhypothalamic transection (*right*). [From Tang & Ruch (32).]

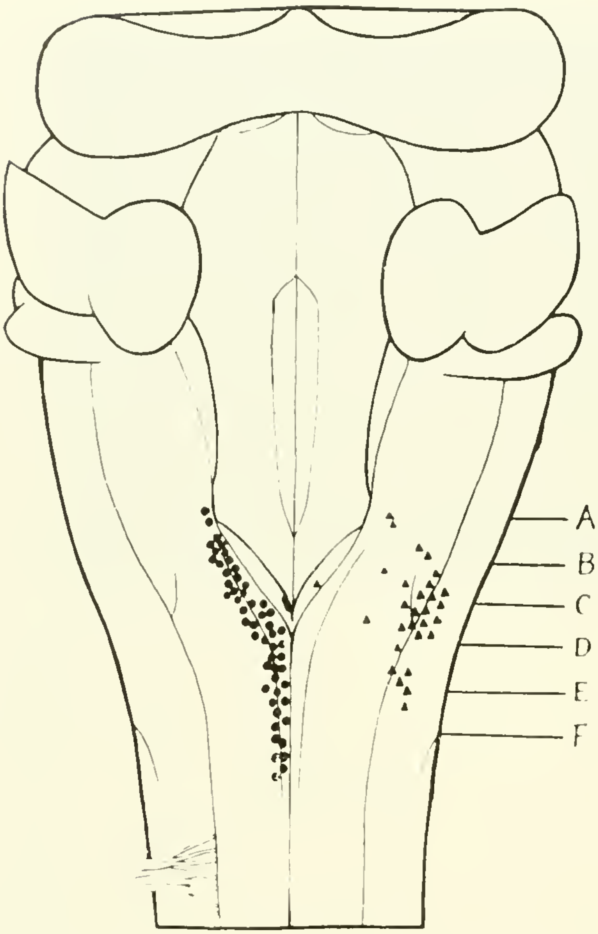

FIG. 17. Dorsal view of the lower brain stem of dog with cerebellum removed. The location of points producing contraction shown by *dots* on the *left*. Points more laterally and deeply located, which relaxed the bladder are shown by *triangles* on *right*. Barbiturate anesthesia and Marey tambour recording. [From Kuru & Hukaya (17).]

is a micturition facilitatory area in its own right or a way station from the cerebral cortex is not clear. Its influence on the bladder is exerted through the sacral nerve roots whereas unsustained contractions may employ sympathetic efferents and may be trigonal in origin.

Since ablation experiments indicate that the bladder, unlike many other viscera, is not represented at the medullary level, interest attaches to the observations of Kuru & Hukaya (17), embodied in figure 17, who found vesicle excitatory points in the medulla. Kuru (16) also traced afferent pathways from the sacral segment to this same region (*vide infra*), suggesting an additional brain-stem level concerned with bladder activity, although presumably not exerting tonic control since subcollicular and spinal transections are equivalent. However, whether fibers of passage or a 'center' was stimulated is not determined.

The two summary diagrams (fig. 18) convey the complexity of descending influences on the micturition reflex. It is a considerably more extensive apparatus than that envisaged by clinical neurologists and urologists. Bladder control is clearly represented at successive levels of the neural axis, just as is the control of somatic reflex activities. It seems unlikely that in man this whole apparatus except its cortical and spinal termini could have fallen into desuetude.

Pathological Physiology of Human Micturition

Only those abnormalities which are neurogenic need be discussed. There are substantial differences in terminology (cf. 20, 23, 25), and terms have been chosen which have unfortunate connotations in respect to neural mechanisms.[8]

UNINHIBITED NEUROGENIC BLADDER (MCLELLAN). Caused by damage to cerebral structures or subtotal interruption of spinal pathways, according to McLellan (20), this condition is characterized by urgency, small-volume thresholds and frequent micturitions that empty the bladder. Continence is usually maintained, perhaps by the external sphincter. Cystometrically, the abortive micturition contractions, accompanied by a desire to micturate, may occur at an initial 25-ml increment and at each subsequent increment; or contractions may not occur until a normal bladder volume is reached but are then imperative. The tonus curve may be within the normal range, or somewhat steep, a change we ascribe to smaller than normal micturition volumes.

This situation is similar to that produced experimentally in cats by intercollicular and transhypothalamic transections. However, the laboratory and clinical workers differ in their interpretation. Clinical accounts emphasize *a*) release of a spinal reflex from cortical inhibition, and *b*) by implication, the corticospinal tract is the inhibitory agent. Neurophysiological experiments suggest that the low threshold and the strength of the detrusor contraction are due, not to the spinal reflex arc's acting alone, but to its

[8] Expressions like 'neurogenic bladder' and 'cord bladder' are clinical jargon, and substitutes should be found. This is apparent if one reflects for a moment on the literal meaning of the phrases.

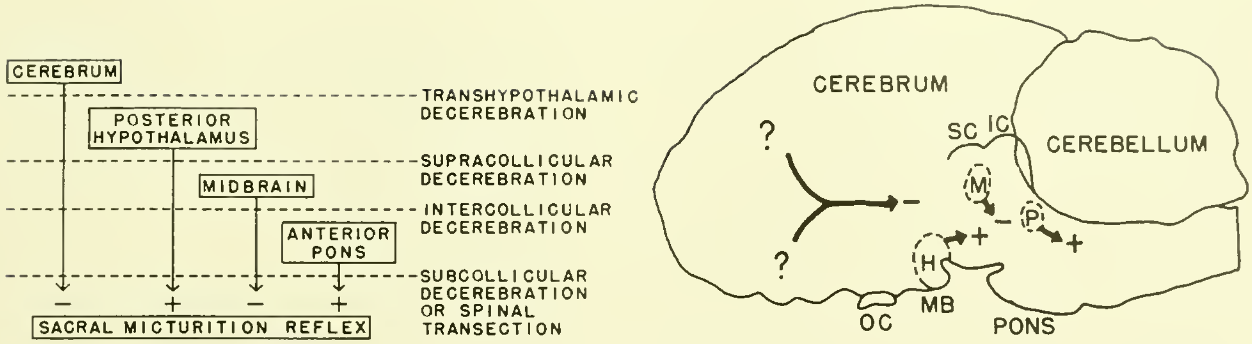

FIG. 18. *Left.* Diagram illustrating the control of sacral micturition reflex by different levels of neural axis, based on cystometric effects of successive removal of these controls by transections at different levels. *Plus sign* indicates a facilitatory and *minus sign*, an inhibitory effect on pelvic nerve preganglionic neurons. [From Tang (31).] *Right.* On a saggital section of the cat brain is projected the loci of the hypothalamic (*H*), rostral midbrain (*M*) and rostral pontine (*P*) areas exerting facilitatory (+) or inhibitory (−) effects on the micturition reflex. Diagram is based upon transections and stereotaxic lesions [From Tang & Ruch (33).]

facilitation from brain-stem centers. The phrases 'facilitated micturition' and 'vesicle hyperreflexia' would convey this better than the clinical phraseology. That the lack of inhibition results from the micturition reflex receiving impulses solely from the pyramidal tract is certainly suspect since activity in other tracts inhibits the micturition reflex after interruption of corticospinal tracts.

From the fact that the bladder, like the antigravity muscles, is subject to a play of facilitatory and inhibitory impulses from the brain stem and cerebral cortex, it appears that the overreactive and the normally reactive bladder represent the retention of some descending facilitatory pathways. This hypothesis is required to explain spastic paraplegia after partial cord lesions and in fact the spasticity of hemiplagia.

AUTOMATIC BLADDER. SYNONOMY: NORMAL AND SPASTIC REFLEX NEUROGENIC BLADDER, SUPRANUCLEAR NEUROGENIC BLADDER, 'CORD' BLADDER. All are agreed that in man, the status of the bladder following immediately and for some days after complete transection of the spinal cord above the sacral segments is one of complete areflexia, although none has offered an explanation of this fact. According to McLellan (20), "Detrusor activity is entirely reflex, micturition being imperative or precipitate, and the ability for its initiation may be lost." Bladder sensation is abolished, although the patient may be aware of the bladder contraction or of concomittant visceral phenomena, flushing, sweating or piloerection. The cystometrogram may approach normal in respect to capacity but not to complete emptying, a residuum of 50 to 100 ml being typical.

A subvariety of the automatic bladder (spastic neurogenic bladder) is described by McLellan as "a spastic, irritable, reflex neurogenic bladder emptying completely at irregular short intervals by precipitate micturition and characterized by a capacity of less than 100 cc. There is usually no warning of evacuation and little inhibitory or voluntary control." This condition is often accompanied by spasticity of the limbs. This category seems to overlap his first one. Munro (23) describes a similar response as the third, or hypertonic, stage preceding the development of a more normal 'reflex bladder.' The inadvisability of designating such bladders as 'hypertonic' has already been discussed.

Neurophysiological and clinical descriptions are not in sufficient rapport to permit a close correlation. However, a few observations and predictions based on general neurophysiological information provide a framework into which the clinical findings might be profitably fitted. The initial stage of areflexia is the first of many parallels that can be drawn between micturition and the myotatic reflex of skeletal muscle on which posture is based. It is probable that interruption of facilitation from higher levels has rendered the local, or segmental, afferent influx from the bladder insufficient to excite the preganglionic sacral neurons. Expressed technically, these neurons, lying in the overlap of descending and segmental synaptic influences, pass from the supraliminal field into the subliminal fringe

and are no longer excited to the point of neuron threshold. Clinical writers are deprived of an explanation for this condition (and offer none) because they recognize no descending facilitation.

The intermediate stage (which may be the final one) of repeated and frequent, although small and abortive or partially effective, micturition contractions is paralleled in the return of myotatic skeletal reflexes. They exhibit exactly the same deficiency in being unable to maintain a strong, sustained reflex (e.g. the knee jerk is present when the paraplegic cannot stand), although as with the micturition reflex, the threshold may be quite low. The end result of a large capacity bladder, as opposed to one with a small capacity, is thus presumed to depend on whether care has prevented those changes in the bladder wall resulting from maintaining the bladder in a state of nearly perpetual, although intermitting, contraction, i.e. unvaried by periodic complete contractions and fillings. Thus, the 'normal' reflex bladder, or Munro's fourth stage, may be simply a bladder which, through avoidance of shrinkage, is able to operate at the higher volumes, i.e. between the normal and the residual volume levels.

Cystitis or the introduction of an irritating solution into the bladder yields a cystometrogram very similar to overreactive neurogenic bladder dysfunction in both man (23; Plum, F., unpublished observations) and animals. This may simply be caused by overactivity of the micturition stretch end organs. Another possibility, which should be explored, is that the bladder possesses a second mode of contraction, allied to nociceptive somatic reflexes which are favored in the spinal state and which are phasic rather than sustained. Such nociceptive reflexes could be operative in both cystitis and after spinal cord lesions.

AUTONOMOUS NEUROGENIC BLADDER. SYNONOMY: INFRANUCLEAR NEUROGENIC BLADDER DYSFUNCTION, DECENTRALIZED BLADDER, DENERVATED BLADDER. This category is well named since remaining bladder function is carried on only by the bladder and the outlying plexus because both the afferent and the efferent parasympathetic limbs of the reflex arc are interrupted by blockade or destruction of the conus medullaris, the cauda equina, the sacral nerve roots, the pelvic nerve or the inferior hypogastric plexus. The terminology assumes that the sympathetic innervation plays no part in the micturition reflex.

Bladder sensation and voluntary and spinal reflex micturition are abolished; the remaining contractions, if any, are small in amplitude, although some authors (9) have reported quite vigorous contractions. The bladder capacity is initially large but returns to or below normal, intravesical pressure is high and small micturitions are frequent. Denny-Brown & Robertson (8) ascribed a considerable part of the activity of the bladder to the intramural plexus, whereas McLellan (20) discounts it. Carpenter & Root (5) recorded autonomous contractions attaining 54 cm hydrostatic pressure, i.e. at the lower range of normal micturition pressures. The cystometrogram is likely to show a steeply ascending tonus limb, the basis of which has been discussed previously. How the physiology of the intramural plexus effects vesical contraction, e.g. whether by axon reflexes or by a synaptic connection between sense organ and postganglionic effectors, has received little attention. The contractions occur after pelvic nerve section and degeneration of most of the afferent supply to the bladder, a fact which argues against axon reflexes of one type. Contractions do not occur after sacral posterior root section; they may be myogenic.

TABETIC BLADDER. SYNONOMY: ATONIC NEUROGENIC BLADDER. An interruption of the sacral posterior roots leaving the motor roots intact completely abolishes the desire to micturate, although a vague awareness of bladder fullness may persist. Reflex contraction of the detrusor muscle fails, and there is a high residual overflow incontinence and a thinning rather than a hypertrophy of the bladder wall. No satisfactory explanation for the absence of activity in the intramural plexus has been evolved. The state is comparable to the absence of the skeletal myotatic reflexes when their posterior root innervation is destroyed. The atonia, as we have seen, is secondary to the failure of the micturition reflex and results from overdistention.

CONTROL OF BLADDER SPHINCTERS

The act of micturition involves an interplay of the detrusor muscle, the internal sphincter, the external sphincter (striate muscle), and striate accessory muscles of the abdominal wall and the pelvic floor.

The internal sphincter is not an anatomical sphincter in the sense of being a distinct, circularly arranged, smooth muscle. Rather, it is a 'physiological sphincter' composed of extensions of the trigonal and mural musculature, sweeping over and under

the internal urethral orifice. The internal sphincter does not act like a gate at the command of the brain. Much of the information on vesical action was provided by Denny-Brown & Robertson (7, 8) who recorded the pressure in the bladder and distal to the internal sphincter in man. The internal sphincter cannot be voluntarily opened or closed independently of detrusor contraction and relaxation, respectively. The external sphincter cannot be voluntarily opened, but it can be closed vigorously in the face of detrusor activity. The internal sphincter cannot be forced by straining (increased intra-abdominal pressure) nor does it open before or immediately when detrusor activity begins. It opens later after a variable rise in pressure (18 to 43 cm), i.e. after an initial period which might be termed the 'initial isometric phase of vesical contraction.'

The internal sphincter is therefore not a primary agent, but it opens sequentially to detrusor contraction and closes sequentially to detrusor relaxation. (Although a constrictor action is exerted by the hypogastric nerve, it is believed to be a part of the act of ejaculation, preventing reflux into the bladder.) Thus, there is little evidence that the internal sphincter is relaxed by either the sympathetic or parasympathetic innervation as a part of micturition, but see Evans (10). The mechanism of the internal sphincter remains speculative. The contraction of the detrusor musculature in the bladder and sphincter may open the sphincter orifice in a mechanical fashion, although this is difficult to visualize from the anatomical arrangements. Or, as the detrusor is activated, impulses may spread through the intramural plexus, relaxing the sphincter. Or, a spinal reflex may sequentially activate the two muscles, a mechanism analogous to that of the cardiac sphincter of the stomach. The latter explanations assume that the sphincter, unlike the mural muscles, possesses neurogenic tonus when, in fact, it restrains fluid under pressure during normal filling when the bladder wall is acting passively or when extrinsic neural activity is in abeyance, as in the acute phase of spinal shock or after sacral nerve section. The mechanical hypothesis is perhaps the most economical.

During micturition, the external sphincter apparently opens as a result of central inhibition of the motoneurons of the pudendal nerve. Evans (10) noted a cessation of nerve impulses in the pudendal nerve when the external sphincter opened as a part of micturition. The tone of this sphincter, like that of other striate muscle, is maintained by a continuous stream of impulses which are inhibited centrally as a part of reflex micturition.

AFFERENT BASIS OF MICTURITION

Vesical afferents and their pathways complete the segmental and supraspinal control of the bladder. When Iggo (12) introduced fluid into the bladder at such excessively high rates that it was filled to its capacity in less than half a minute, single afferent neurons in the pelvic nerve discharged occasionally, i.e. irregularly, beginning at about 20 ml of volume. The discharges accelerated briefly to a maximum of 20 to 30 per sec. (at about 40 ml of fluid) and then decelerated to 1 per sec. despite further filling. During sustained, but not increasing, filling approaching micturition threshold volume (30 to 60 ml), the frequency was very low (4 to 6 per min.). This suggests either that the end organs adapt rapidly or that the internal viscous flows end the stimulus. Although the evidence is fragmentary, there presumably is only a slight discharge during the initial phases of the cystometrogram, not sufficient in itself to induce reflex micturition in the normal animal but sufficient when the preganglionic fibers are heavily facilitated from above as in the intercollicular or transhypothalamic decerebrate preparation when the micturition threshold is low and the resistance to passive stretch is like that in the normal animal.

The micturition reflex is perhaps the longest sustained phasic spinal reflex. If this long duration is gained peripherally, a certain arrangement of stretch receptors can be predicted. If the stretch receptors are arranged in parallel with the muscle fibers, their shortening would slacken them, ending the stimulus to the receptor and to the continuation of micturition. On the other hand, if the receptors are arranged in series, isometric and even isotonic contraction should increase the rate of firing during detrusor activity. In a chloralosed cat, the bladder distended with 5 to 15 ml of water characteristically contracts rhythmically, although not strongly. A few impulses at low frequency occurred in a single fiber as fluid returned to the bladder (fig. 19, lower record). As the bladder contracted, there was a sudden increase in the rate of firing which stopped completely when the bladder started to relax. When flow of fluid from the bladder was restrained, firing coincident with contraction was sharply increased (from 5 per sec. to 30 or 40 per sec.), and the discharge was sustained at a high rate, 20 per sec., for as long as half

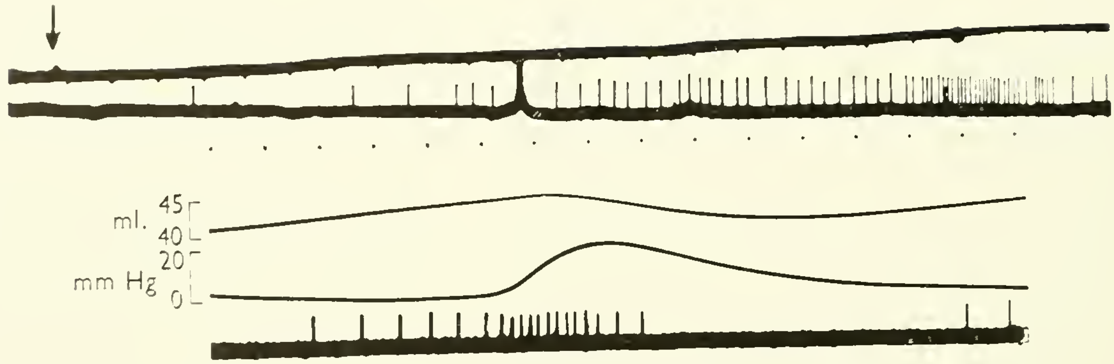

FIG. 19. *Upper record.* Impulses in single afferent fiber of the pelvic plexus (*lower trace*) aroused by exceedingly rapid passive filling of denervated cat bladder. *Upper trace* shows the intravesical pressure. Time pips at 1-sec. intervals. *Lower record.* Impulses in a pelvic afferent fiber due to a 'spontaneous' contraction during emptying and filling. *Lower trace*, action potentials; *middle trace*, intravesical pressure; *upper trace*, bladder volume. Note emptying is downward. [From Iggo (12).]

a minute. The same afferent neuron discharges to passive stretch and, more vigorously, to the active tension of isometric contraction of the bladder muscle; the neuron also discharges to the actual shortening of the fibers but not to their lengthening during relaxation.

This behavior is consistent with a stretch receptor arranged in series with the muscle fibers and accounts for the sustained character of micturition, but it may not be the only mechanism. The complex brain-stem mechanism for bladder controls suggests that afferent impulses from the bladder may be 'long-circuited' through the brain where circularly arranged nerve nets would provide the temporal dispersion of impulses returning to the segmental preganglionic neurons. Whether this is the case will not be known until input-output studies are made.

Spinal Afferent and Efferent Pathways

The spinal afferent pathway of the bladder in animals is difficult to distinguish experimentally from the descending pathways, but in man, bladder sensations provide additional information. While anterolateral cordotomy in man often interferes transiently or even permanently with bladder function, well-executed cordotomies induce little or no bladder disturbance, either sensory or motor. Ascending impulses from the bladder apparently do not follow the same pathway as sensations of the sexual orgasm which are abolished by cordotomy. The lamination of the spinothalamic tract would predicate a posterolateral locus of ascending fibers. The available experimental evidence (3) suggests that bladder afferent and motor spinal tracts occupy an even more posterolateral position, i.e. superficially just ventral to the posterior horn. A dorsal quadrant section of the spinal cord in the cat seems almost equivalent to a spinal cord section in severity of bladder disturbance. McMichael (21) described a critical case of severe bladder disturbance, unaccompanied by somatosensory disturbance, in which the lesion was restricted to the superficial fibers in the extreme posterior portion of the posterolateral column (fig. 19). Nathan & Smith (24) place the ascending fibers somewhat more ventrally where they would almost certainly be injured by cordotomy which often does not occur. White (35) suggested that the posterior columns may conduct sensory impulses from the bladder, and Talaat (30) confirmed this electrophysiologically.

In tracing the ascending degenerations in Marchi preparations of cordotomy cases, Kuru (16) described, under the name tractus sacrobulbares, fibers pursuing the same general pathway as the spinothalamic tract, some terminating in the juxtasolitary nucleus and some dorsal to its rostral end. Sacral components in the posterior column were traced to the same general area. Continuation of the system by second- and third-order neurons could reach the pontine bladder-controlling area which acts when rostral connections are severed. In this fashion, a controlling circuit starting and ending in the bladder would be closed.

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CHAPTER XLIX

Reproductive behavior

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CHAPTER CONTENTS

THE INFLUENCE OF INTERNAL SECRETIONS on nervous function is nowhere more pronounced than in the dramatic effects of sex hormones on reproductive behavior. Patterns of courtship, mating and parental behavior have been described extensively and have been shown to be activated by hormones in both invertebrate and vertebrate phyla. The present paper will not attempt to review the multitude of interesting behavioral sequences in the lower animal forms; for accounts of these, reference is made to the monograph by Tinbergen (92) and to the excellent reviews of Beach (10, 11). The present work will concentrate on the far better known mammalian patterns, their anatomical and physiological neural correlates, and mechanisms of neuroendocrine interaction.

Many of the more active research contributors to this field have published authoritative reviews of their own extensive studies. In order to keep the present list of references within reasonable limits much of the work of these investigators will receive reference through their reviews rather than their original individual publications.

HISTORICAL BACKGROUND

Early in the nineteenth century Gall and Spurzheim (87), as part of their phrenological considerations, located a center of sexual behavior or 'amativeness' in the cerebellum. This concept has never been supported by evidence from animal experiments. In his now famous experiments on the dog brain Goltz (36, 37) reported that the cerebral cortex was an essential substrate for sexual behavior in the male but not in the female. Electrical stimulation experiments by von Bechterew (93) supported the cortical location of a center controlling erection and ejaculation in dogs. In 1900 Sherrington (86) described reflexes related to sexual activity in spinal dogs. Around the turn of the century Steinach (89) stressed the dependence of sexual behavior on the stimulating action of gonadal internal secretions on the nervous system.

During the first half of the twentieth century a few investigators should be cited for the considerable influence of their research on the field of reproductive behavior. Marshall (64) emphasized the importance of exteroceptive factors such as light and temperature on sexual periodicity. From the 1920's Stone (90) observed that rabbits and rats with large cortical lesions remained sexually potent and active. Bard (5, 6) has made a careful study of the sexual capacities of cats with well delineated lesions in various cortical,

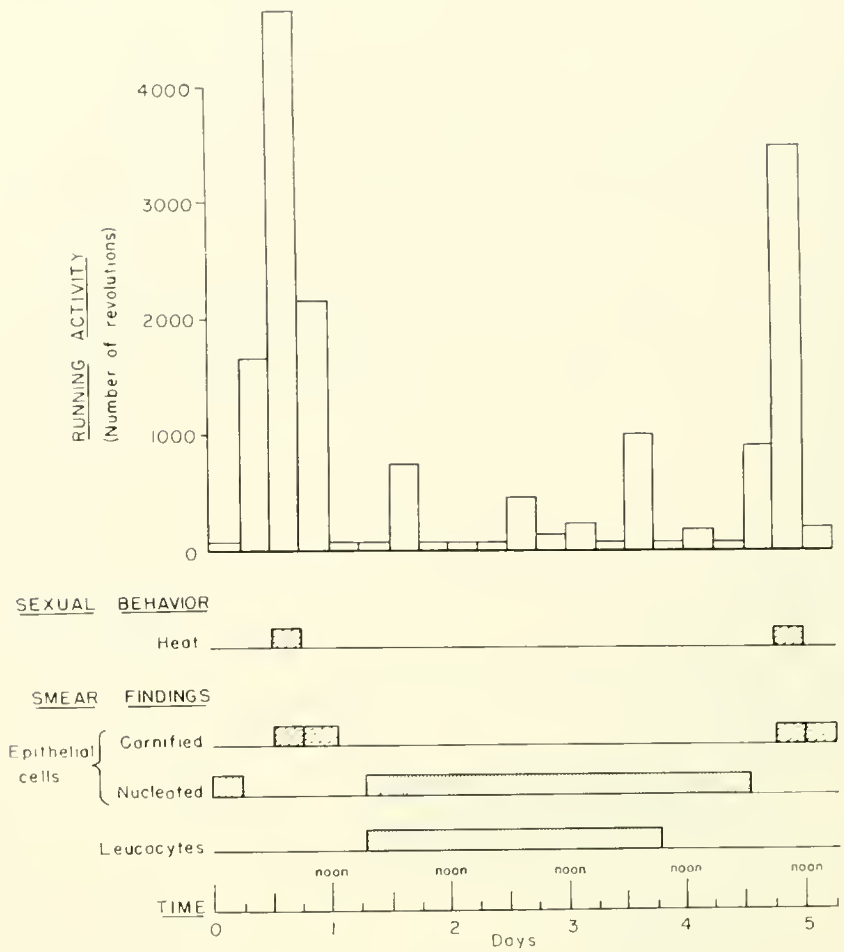

FIG. 1. Relationship between running activity and vaginal and estrous cycles in the rat. [Adapted from Wang (94).]

subcortical and spinal regions. The effects of genetic background and psychological determinants as well as hormonal influences on quantitative differences in mating behavior have been the province of Young (97, 98). Beach (10–13) has studied the effects of castration and replacement therapy and has analyzed the results of cortical lesions placed at various developmental periods in the brains of several mammalian forms. Purportedly quantitative reports on human sexual activities have been presented by Kinsey (51, 52).

METHODS OF ASSESSING SEX DRIVE

Stone (90) has defined sex drive as "aroused action tendencies in animals to respond to objects of their external environments that, in some measure, lead to the satisfaction or alleviation of dominant physiological 'urges' associated with reproduction." The relative merits of modern techniques for assessing this abstract force in quantitative terms have recently been reviewed by Beach (13), Richter (73) and Young (98).

Early in the 1920's a striking correlation between the periods of estrus and running activity in the female rat was observed by Wang (94) (fig. 1). In periods of anestrus due to pregnancy, pseudopregnancy or lactation, running activity remained at a minimum.

Ball (4) devised a test of sexual receptivity for female rats in which their response to manual stimulation was graded on a 10-point scale. She was able to relate excitability scores with degrees of responsiveness to the male rat, with changes in the vaginal mucosa, and with onset, duration and termination of

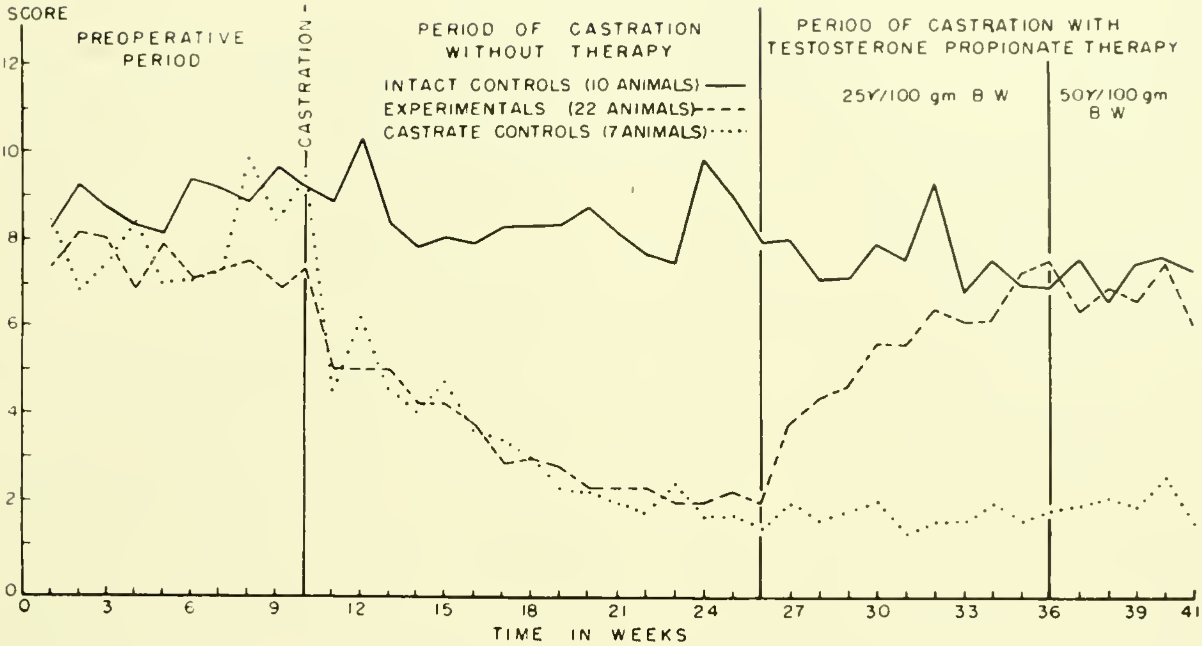

FIG. 2. Effects of castration and therapy with testosterone on sex drive in the male guinea pig. [From Grunt & Young (43).]

estrus. More recently Goy and Young (98) have described several measures of receptivity in the guinea pig, including latency of estrus after hormone treatment, duration of estrus, duration of maximum lordosis, frequency of male-like mounting and per cent of animals brought into heat by the treatment.

Similarly in the male guinea pig Grunt & Young (43) have evolved a quantitative measure of sex drive based on counting and weighting arbitrarily the following activities during a 10-minute period in the presence of an estrous female: nibbling, nuzzling, mounting, intromission and ejaculation. An example of the use of this scoring method appears in figure 2. Similar methods have been employed with male rats (13).

Other assay methods which have been employed in studies on male experimental animals have also been reviewed (13, 35, 85); these include the use of mazes, runways, Skinner boxes and various electrical shocking devices. The readiness with which a male rat will learn to run a T-maze for an estrous female as the reward may be extrapolated to test motivation. With a receptive female as the object, the rate of bar pressing by a male rat in a Skinner box has been observed to correlate with its presumed level of sex drive. The running speeds of male rats, guinea pigs and dogs along alleys or over hurdles and the persistence of males in crossing an electric grid to reach estrous females have been observed to be positively related to sexual performance.

ENDOCRINE, GENETIC AND SOCIAL FACTORS IN SEX BEHAVIOR

The effects of castration in the male depend on the species, the relative age of the individual at surgery and his previous sexual performance. In general the changes in behavior are similar to those illustrated for the guinea pig (fig. 2) by Grunt & Young (43). There is a gradual loss in sexual activity, with the processes of ejaculation and intromission disappearing earlier than the less consummative phenomena. Similar effects have been reported in dogs (13, 35) and cats (41). In the adult human (90) castration may be followed by little or no perceptible loss in sexual performance.

Replacement therapy with testosterone rapidly restores sex drive to animals in which castration has reduced it. In the guinea pig (fig. 2) raising the androgen dosage above the minimum needed to restore the preoperative behavior level does not result in increased performance. In the rat, however, testosterone dosages higher than the maintenance level

induce still further improved performance, indicating a species difference (35).

As compared with the slow gradual loss of sex behavior in male animals on castration, the loss of receptivity and estrous cycles on ovariectomy in females is immediate and practically complete. Of the common laboratory animals only the female rabbit will occasionally remain receptive after castration (45). The wide variety of female copulatory behavior patterns in the common domestic and laboratory species has been described by Young (97). Typically, the female depresses her back and raises her pelvis in a lordosis response and, after intromission, remains quiescent as in the rabbit or undergoes a more or less violent rolling, rubbing, squirming after-reaction as seen in the cat.

Many ovariectomized forms, including the dog, cat and rabbit, can be restored to a state of practically complete estrus with estrogen alone. Even in these forms the degree of heat may be temporarily elevated still further with progesterone. Rats, mice, guinea pigs and hamsters ordinarily require progesterone following estrogen priming to induce a receptive state (21). In the hamster the combination is needed to subdue the female's aggressiveness as well as to promote estrus (53). The period of estrus induced by the combination of steroids is limited to a few hours after which the animal is decidedly nonreceptive and, in the case of the hamster, very aggressive. This anestrous phase following progestrone treatment has been emphasized to the extent that some authors have disregarded the earlier estrous phase.

Among the lower forms such as the rat, guinea pig and rabbit, each sex has the inherent capacity for performing the copulatory pattern of the opposite sex (10, 35, 97). The female rat may show mounting behavior at any time during the estrus cycle or even after ovariectomy, whereas the female guinea pig and rabbit reveal male behavior only at the height of natural or estrogen-progesterone induced heat. Similarly, a male rat on an overdosage of testosterone may show the female pattern. With threshold hormonal complements, intrinsic or exogenous, each sex appears to prefer its own behavior pattern; with superthreshold levels it is prone to perform the pattern of the opposite sex, especially in the presence of individuals of its own sex.

Further evidence of the nonspecificity of sex hormones comes from experiments in which castrate females have been treated with testosterone and castrate males with estrogen. Whereas in the prepuberal state each hormone does tend to induce the behavior characteristic of its sex regardless of whether the recipient is male or female, adult castrates usually regain their sex-specific behavior pattern whether treated with estrogen or testosterone (10, 41). In the ovariectomized rabbit Klein (55) reports that testosterone pellets maintain a highly estrous condition indefinitely. Such treatment leads to an aggressive attitude towards other females (Kawakami & Sawyer, unpublished observations), thus differing from natural or estrogen-induced heat.

Complete mating behavior patterns do not appear to be innate in any of the common laboratory species with the possible exception of the rat (98). Guinea pigs, dogs, monkeys and chimpanzees reared in isolation all showed some deficiency in mating as compared with controls of equal age brought up in association with other members of the same species.

Male animals of many species adopt a territory in which they will mate readily and out of which they show extreme reluctance to copulate. In the laboratory this is especially true of cats (41) of which more will be discussed below.

Beach (13) has recently proposed that mating behavior in the male rat consists of two principal processes: an arousal mechanism, and an intromission and ejaculatory mechanism. Electroconvulsive shock inhibits the arousal mechanism but facilitates the ejaculatory process (35).

The hormonal requirements or accompaniments of maternal behavior have been studied extensively in rats (11, 96). Such activities as nest building, retrieving and cuddling newborn young are dominant during late pregnancy and lactation. Rats at this stage may 'mother' an adult mouse (49). Estrogen appears to inhibit maternal responses (44) even in dosages too small to interrupt lactation (95). Anterior pituitary extracts were found to induce adult virgin rats to retrieve newborn young (96). Riddle *et al.* (74) showed that an appropriately timed injection of prolactin would evoke maternal behavioral activities in a high percentage of their virgin female rats.

NEURAL MECHANISMS AND CENTERS AS REVEALED BY LESION EXPERIMENTS

As in other types of behavior patterns, reproductive behavior involves afferent, central and effector mechanisms. Various components of the patterns of the two sexes have been ascribed to different functional levels within the central nervous system, and considerable research has been aimed at locating the sites of 'sex

centers' within the brain and spinal cord. A 'center,' as the term will be employed here, is a locus of integration of the component activities of a total pattern. Destruction of the center may leave individual components or lesser complexes of the pattern intact. The center may be influenced by afferent or humoral mechanisms or both from the periphery or by projections from higher levels but is capable of basic independent activity after extirpation of higher controls. The principal 'sex center' would be the critical area influenced by sex hormones to evoke patterns of reproductive behavior, the destruction of which would eliminate such behavior patterns.

Peripheral and Spinal Mechanisms

It is remarkable how relatively unimportant the afferent impulses from genitalia are in maintaining sex behavior in lower mammals. Anesthetizing (29a) or deafferenting the vagina (18) or surgically removing the vagina and uterus (3) have not prevented mating in rabbits and rats. Female cats retain estrous behavior after removal of the sacral region of the spinal cord or the abdominal sympathetics (5).

Similarly in the male cat Root and Bard (6) have found that anesthesia of the penis and perineum through surgical removal of the lower end of the spinal cord does not diminish sexual aggressiveness. In the presence of an estrous female, such a cat develops an erect penis and attempts copulatory movements. The addition of sympathectomy to the cord injury removes the power of erection but not the attempts to copulate. Beach and his colleagues (12) have shown that elimination of the penile bone in the rat, either surgically or through castration on the day of birth, interfered with the achievement of copulation but not with attempts to copulate. Their results reveal that regardless of the influence of hormones on genitalia a neural site of hormone target action central to the peripheral sense organs is capable of maintaining sex drive. Genital sensation may, however, strengthen the force of the drive.

Spinal male animals of several species including the dog and man maintain the capacity of penile erection and ejaculation on manipulation of the genitalia (32, 86). In male cats after spinal transection a type of flexor rigidity reminiscent of mating posture was described by Dusser de Barenne & Koskoff (26, 27). Accompanied by erection this reaction was suggestive of a spinal copulation reflex, but it could hardly qualify as real mating behavior.

Spinal female animals can be impregnated, can maintain pregnancy and can deliver normal litters, as first described in the dog by Goltz (36). These observations, however, are less concerned with behavior than with other reproductive phenomena. No change in spinal reflexes in the female guinea pig which could be attributed to the injection of estrogen and progesterone was observed by Dempsey & Rioch (22). A similar failure to observe reflexes which could be altered by estrogen was reported by Bromily and Bard (6) in the spinal cat. These authors found that reflexes, such as tail deviation on prodding the perineum, which had been reported in the decapitate cat as dependent on estrogen (61), could also be elicited in the anestrous female and even in the male cat. It appears that the partial behavioral pattern is present in the spinal cord of either sex, but its differential hormonal activation requires integration from higher centers.

Lower Brain-Stem Mechanisms

Sectioning the brain stem in such a way as to leave the cord, medulla, pons and lower mesencephalon intact results in 'decerebration.' Among the differences between the spinal animal and the decerebrate preparation is the development of rigidity in the latter, and this rigidity might interfere nonspecifically in reproductive behavior patterns. Dempsey & Rioch (22) could find no evidence of estrous behavior in decerebrate female guinea pigs; Maes (61) attributed their failure to observe sexual reflexes, such as treading and elevating the pelvis, to the decerebrate extensor rigidity which they all displayed. However, in decerebrate female cats Bromily and Bard (6) were able to reverse the rigidity and induce a crouching posture by stimulating the vagina with a glass rod. This component of the female cat pattern could not be duplicated in decerebrate bitches, which do not crouch at mating, nor in male cats; but it was elicited in anestrous as readily as in estrous cats. The conditioning influence of estrogen (and progesterone in the guinea pig) would appear to be exerted at some level higher than the plane of decerebration.

Neocortical and Rhinencephalic Mechanisms

The cerebral cortex is relatively unimportant in the maintenance of mating behavior in most female mammals. Rioch and Bard (5) removed increasingly larger portions of the cortex in the cat until all of the neocortex, most of the rhinencephalon, and a large part of the striatum and thalamus had been de-

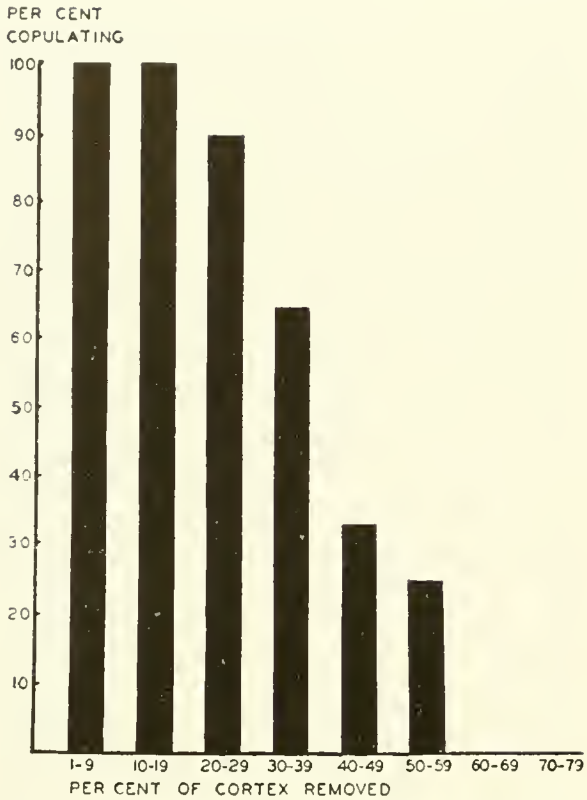

FIG. 3. Effects of partial decortication on sex behavior in male rats; per cent of animals in each lesion group continuing to copulate after operation. [From Beach (8).]

stroyed, without eliminating estrous behavior in response to estrogen. The female rabbit still mates after removal of the neocortex, the rhinencephalic cortex, and the distance receptors of olfaction, vision and audition, the olfactory bulbs, eyes and cochlea, respectively (18). Davis (20) found that removal of the whole neocortex in the rat did not interfere with estrous cycles, mating, pregnancy or delivery, findings which have been repeatedly confirmed (11).

The cortex is essential for the initiation of mating behavior in most male mammals. In the rat, Beach (8) showed that while removal of 20 per cent of the cortex did not reduce the percentage of males showing copulatory behavior, no male mated if more than 60 per cent of its cortex had been destroyed (fig. 3). Similarly, mounting behavior is lost in female rats on decortication whereas their female patterns of activity are retained (9). In these studies the location of the cortical area removed was considered less important than the quantity.

In the male rabbit (18, 90) the destruction of neither the neocortex nor the olfactory bulbs alone prevents courtship and mating activities, but the removal of both olfaction and cortical representation of somesthetic, auditory and visual sensibility terminates sex behavior.

Beach and his colleagues (35) have recently studied in great detail the effects of decortication on reproductive behavior in the male cat. In this species, in contrast to the rat, large cortical lesions do not appear to depress the animal's interest in the female so much as they interfere with motor activity related to copulation. Cats with large frontal lesions would attempt to copulate but would fail to gain intromission in most cases.

The results of decortication experiments reveal that the loss of cortical sensory and motor areas affects male sex behavior patterns more acutely than it does the female activities. In each case the actual execution of mating behavior appears to be controlled by subcortical mechanisms.

A type of rhinencephalic control over sexual behavior, especially in the male, has recently been reported by several investigators. Hypersexuality in the male monkey as a result of removal of the temporal lobes was described by Klüver and Bucy in 1939 (56). Schreiner & Kling induced hypersexuality in the cat, agouti, monkey and lynx by removal of the amygdala and the overlying piriform cortex and demonstrated its dependence on the male sex hormone (82–84). Similar changes have been reported in man (76, 91).

Green *et al.* (41) have made a careful study of experimental hypersexuality in the cat, observing the effects of small electrolytic and surgical lesions in the amygdala, hippocampus, piriform cortex and stria terminalis. They were unable to produce hypersexuality by destruction of the amygdala alone; but small lesions in the piriform cortex, restricted to an area just medial to the rhinal fissure and beneath the basolateral amygdaloid nucleus, induced hypersexual changes without damage to the amygdala (fig. 4). The cats with such lesions were active and alert and would mate in a strange territory, a procedure not commonly practiced by apparently hypersexual cats without lesions. Castration slowly reduced the hypersexuality, but it could be restored with either androgen or estrogen.

Hypersexuality was not observed in female cats with amygdala-piriform-cortex lesions by Schreiner & Kling (82–84) or Green *et al.* (41). Gastaut (33) described estrous activity in cats with rhinencephalic lesions in which the reproductive tract appeared anestrous. Female rabbits with lesions in the septum,

fornix or amygdala-piriform-cortex appeared to mate normally, but not in a hypersexual manner, and to ovulate in response to such mating (78).

Diencephalic and Hypothalamic Mechanisms

The mechanisms discussed above have pointed to the diencephalon as the site of 'higher centers' with reference to the cord and lower brain stem, and 'subcortical centers' with reference to the cerebrum. Since integrated estrous behavior can be evoked in the absence of the cerebrum but not in animals with brain-stem transection below the midbrain, the highest essential center for estrous behavior would appear to lie between the rostral midbrain and the preoptic region.

Large thalamic lesions in connection with cerebral damage did not eliminate sexual behavior in the female cat (5). Dempsey and Morison [discussed in Beach (12)] removed the thalamus bilaterally in cats that later mated, maintained pregnancy and delivered young but failed to care properly for them. Large thalamic lesions did not prevent mating or ovulation in the rabbit, according to Sawyer (unpublished observations).

Among the earlier hypothalmic lesions with a bearing on the problem were those of Ranson (71) who reported that female cats with tuberal lesions behind the infundibulum mated and gave birth to litters. Later work in Ranson's laboratory (31) showed that female cats with lesions in the anterior hypothalamus around the supraoptic nuclei did not mate. This was confirmed by Dey *et al.* (23), and Brookhart *et al.* (16, 17) showed that estrogen treatment would not induce receptivity in guinea pigs with anterior hypothalamic lesions. Maes (62) demonstrated that in estrogen-treated female cats the pituitary gland was unnecessary for apparently complete mating behavior.

An observation of considerable influence was made in 1939; Dempsey & Rioch reported (22) that brain-stem transection rostral to the mammillary bodies was consistent with mating while similar section behind the mammillary bodies resulted in anestrus. Actually the definite results were obtained with one guinea pig and one cat. In the light of these findings Bard (6) interpreted the hypothalamic lesions of Magoun and Bard as indicating that the highest center of sex behavior in the cat lay in the rostral mesencephalon. However, as indicated below, the evidence of Magoun and Bard is consistent with the presence of a sex center in the anterior hypothalamus.

Sawyer & Robison (81) have recently found in female cats that anterior hypothalamic lesions rostral to the ventromedial nuclei and either medial to or within the area of the medial forebrain bundle result in permanent anestrus in 11 out of 14 cases in spite of treatment with exogenous estrogen. Such lesions do not interfere with the trophic influence of the hypophysis on the ovary, and ovulation can be induced by direct electrical stimulation of the ventromedial nucleus. Lesions in the ventromedial nucleus, the premammillary region or those entirely destroying the mammillary body result in anestrus due to ovarian atrophy from pituitary hypofunction. However, if such cats are supplied with exogenous estrogen, they show all the usual behavioral responses of mating and after-reaction. Typical lesions are illustrated in figure 5. The results confirm the findings of Ranson's laboratory and do not support the work of Dempsey & Rioch (22) in the cat. Bard's (6) figures reveal destruction of the anterior region in a cat which would not mate and the sparing of this region in a lesion-bearing cat that subsequenty became receptive on estrogen treatment.

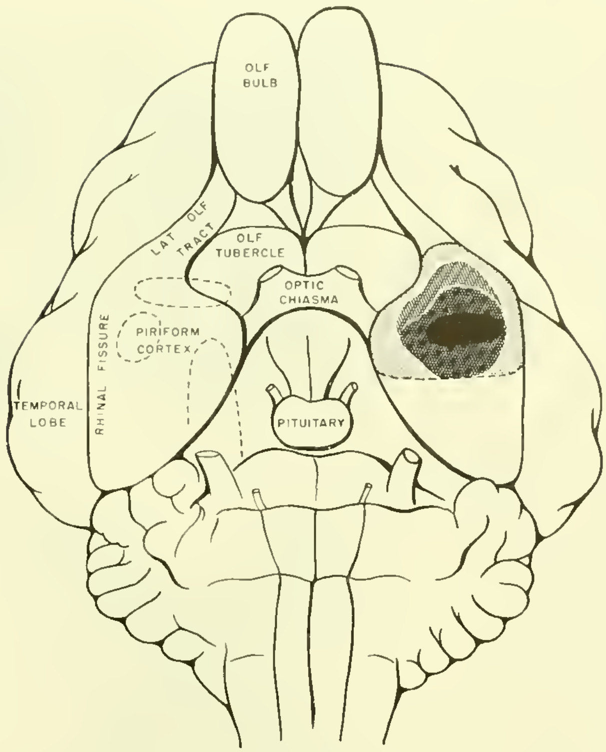

FIG. 4. Base of the cat brain showing the area in piriform cortex (*solid black*) in which lesions most consistently induced hypersexuality in males. [From Green *et al.* (41).]

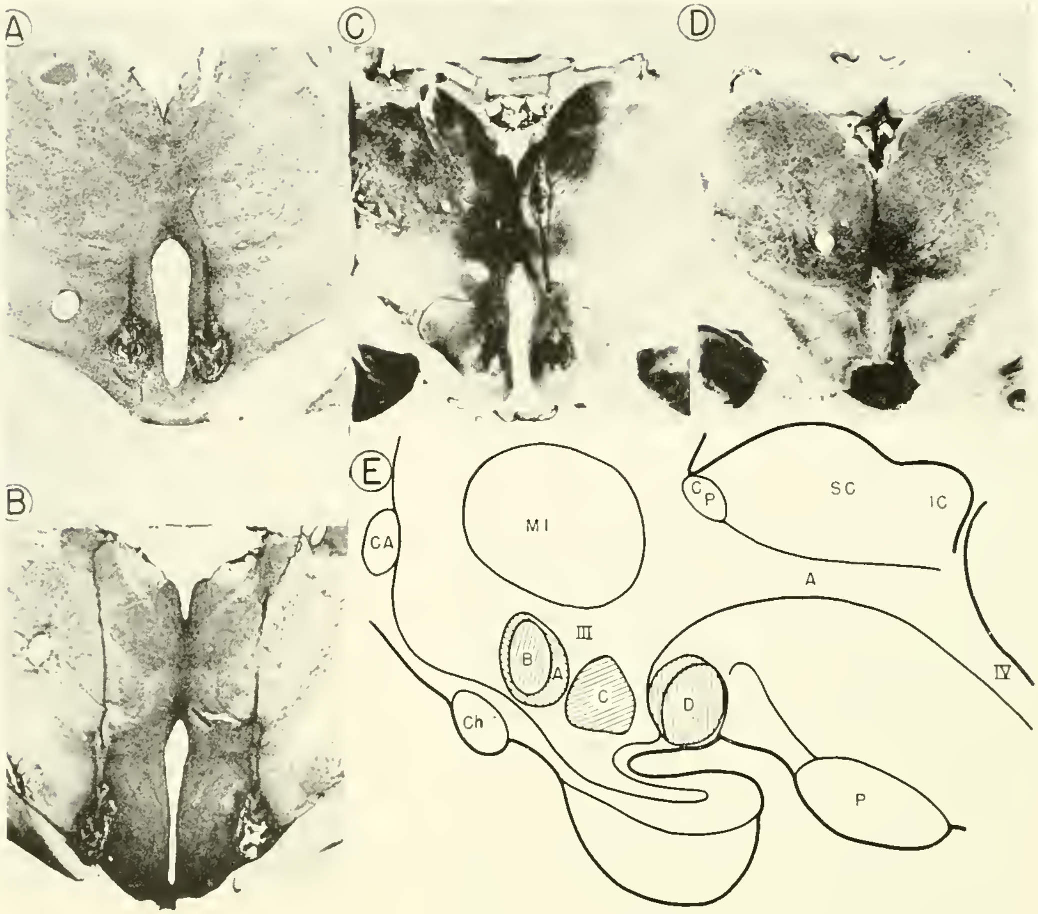

FIG. 5. *A*, *B*. Anterior hypothalamic lesions which induced permanent anestrus in the female cat in spite of treatments with exogenous estrogen. *C*. Ventromedial lesions which induced ovarian atrophy but did not abolish mating behavior if exogenous estrogen was supplied. *D*. Mammillary lesions with same effect as in *C*. *E*. Midsagittal reconstruction showing anterior-posterior extent of lesions *A* to *D*. [From Sawyer & Robison, unpublished observations.]

Interestingly enough the female rabbit does appear to have an hypothalamic mating center (78, 79) in the region proposed by Dempsey and Rioch for the guinea pig and cat. Small bilateral lesions in the mammillary region induced permanent anestrus which could not be reversed with exogenous estrogen. The ovaries remained in good trophic condition, and they could be ovulated by artificial activation of the hypophysis. On the other hand, rabbits with ventral tuberal lesions involving the arcuate and base of the ventromedial nuclei mated but failed to ovulate. Some of the latter cases revealed ovarian atrophy, and they required exogenous estrogen to stimulate receptivity (fig. 6). These experiments do not exclude the possibility of anterior hypothalamic involvement in mating behavior in the rabbit; animals with anterior lesions did not survive long enough to be tested for the mating response. In both the rabbit and the cat it is apparent that the common basal tuberal area which controls the release of pituitary ovulatory hormone is not a center of influence on mating behavior but that a behavioral center exists rostral to this region in the cat and caudal to it in the rabbit.

A similar duality of gonadotrophic and sex behavioral centers in the male has recently been reported for the rat by Rogers [quoted by Goldstein (35)]. Premammillary lesions reduced mating behavior but it could be restored with gonadal hormones. Rats with 'tuberal lesions' showed a behavioral loss which could not be reversed with androgen. These

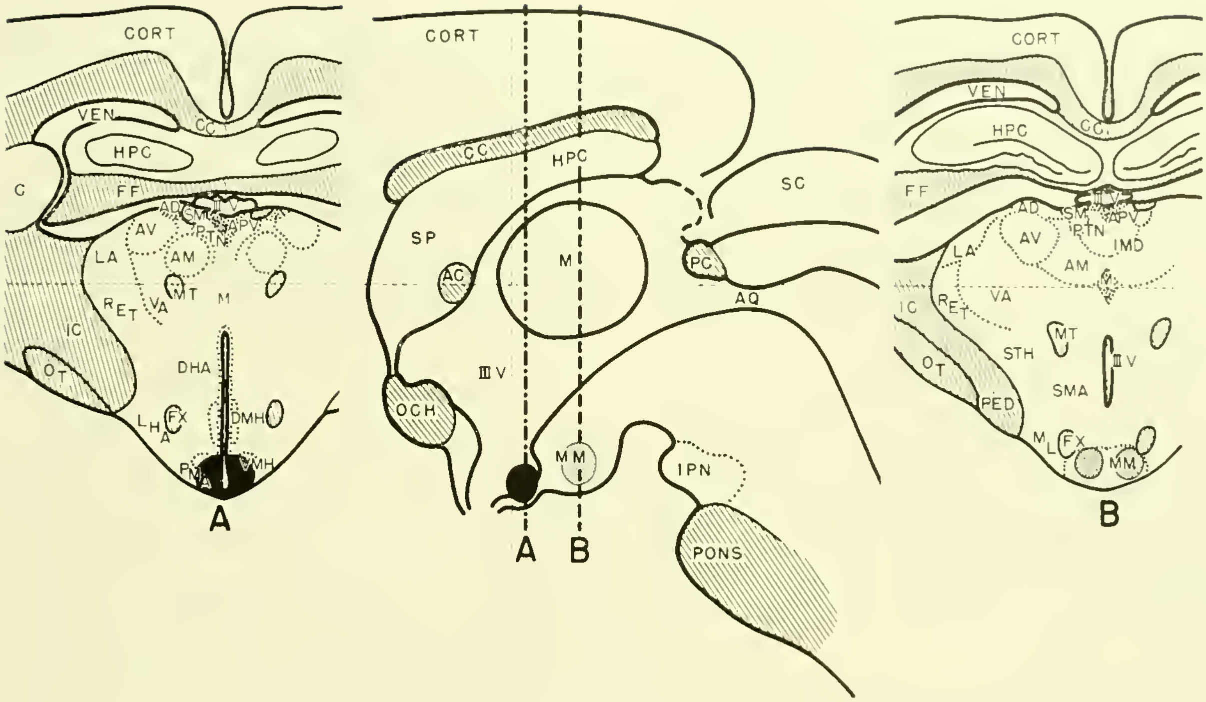

FIG. 6. Sites of hypothalamic lesions in the female rabbit brain. Mammillary lesions at *B* (*stippled*) abolished mating behavior in spite of therapy with exogenous estrogen but did not induce ovarian atrophy. Tuberal lesions at *A* (*solid black*) blocked copulation-induced ovulation or led to ovarian atrophy but did not diminish receptivity if extrinsic estrogen was supplied. [From Sawyer (79).]

latter sites of local damage perhaps correspond to the anterior hypothalamic lesions of Brookhart & Dey (15) which irreversibly eliminated sex behavior in the male guinea pig without damaging the testes.

Sexual precocity of cerebral origin may result from lesions such as tumors originating within the hypothalamus or damaging hypothalamic areas from above, as in the case of pinealomas (7). Accelerated sexual development through increased gonadotrophic secretion may not be accompanied by precocious sexual behavior, a further indication that gonadotrophic and sex behavioral centers are not identical. Hillarp *et al.* (48) have described preoptic lesions in rats of either sex which temporarily stimulate compulsive male mating behavior. Harris and his colleagues have suggested that the anterior hypothalamus in ferrets and rats contains a center inhibitory to the release of pituitary follicle stimulating hormone (24, 25, 46). Lesions in this area accelerate the onset of seasonal estrus in mature ferrets and the opening of the vaginal orifice in young rats.

Effects of Nerve Lesions on Maternal Behavior

No systematic studies have been made of the effects of nervous lesions on maternal behavior except in the rat. Female rats rendered anosmic and deaf by Wiesner & Sheard (96) still built nests and retrieved young. More recently Beach & Jaynes (14) have shown that rat maternal behavioral responses survive enucleation of the eyes, removal of the olfactory bulbs or destruction of sensory nerves to the snout. Removal of all three afferent pathways, however, completely inhibited maternal care of the young, and the combined destruction of any two sensory routes seriously interfered with maternal behavior.

In 1937 Beach (11) reported that removal of more than 30 per cent of the cerebral cortex delays nest building in the pregnant rat and subsequently decreases its ability to retrieve and care for its litter. Stone (90) and Davis (20) confirmed the finding that large cortical lesions interfered with maternal behavioral performance. All of these investigators stressed the relationship between the size of the lesion

and debility rather than the importance of the location of the lesion. More recently Stamm (88) has reported that relatively small lesions, involving only about 16 per cent of the cortex, located medially in the cingulate and retrosplenial cortex, interfere very seriously with litter survival, nest building and repair, retrieving young, and removing them from excessive heat. Similarly sized lateral lesions were without apparent effect. Electroconvulsive shock treatment from the 12th day of pregnancy to parturition in rats obliterates nest-building behavior and care of the litter (75).

In its dependence on the cortex, female maternal behavior more closely resembles male mating behavior than female psychic estrus. Female mating behavior depends less on initiative and distance receptors than on proprioception, tactile sensation and an elevated hormone titer. The reverse is true in maternal behavior, maze learning and male reproductive activities.

NEURAL MECHANISMS AND CENTERS AS REVEALED BY STIMULATION AND RECORDING EXPERIMENTS

Peripheral Mechanisms

Although only a minimum of afferent innervation appears to be necessary to maintain reproductive behavior, especially in female animals, the influence of sex hormones on receptors must be considered as, at least, auxiliary mechanisms in sex drive.

Beach (12) and Holz have shown that castration in male rats on the first day of life leads to the development of a penis too short to permit normal reproductive behavior on subsequent treatment with testosterone. Castration in the adult rat results in a penis with a reduced number of genital papillae, making it a less sensitive tactile organ (12).

Campbell *et al.* (19, 54) have studied the receptors and afferent nerves in the penis and clitoris of cats, cattle and sheep by anatomical and electrophysiological methods. They propose, as an hypothesis, that altered sensitivity during tumescence of the genitalia is modulated by an effect of the deep encapsulated end organs on the fine nerve fibers emerging from them.

Partial patterns of sexual behavior in estrous female animals can be evoked by grasping the neck or back and prodding the perineum with a glass rod. As mentioned above, responsiveness to such treatment has been made the basis of quantitating female sex drive in rats by Ball (4). Artificial stimulation of the vagina induces a species-specific after-reaction which is followed by ovulation in the cat (42) or the estrogen-treated rabbit (77; see also below).

There is evidence that olfactory sensibility plays a unique role in sexual behavior. Le Magnen (57) has reported that, correlated with estrogen and androgen titers in rat and man, there are marked alterations in the subject's ability to detect odors of synthetic musk and urinary steroids. These 'olfactosexual' phenomena appear to be of more importance in the lower mammal (57).

Hypothalamic Mechanisms

The diencephalon contains centers in which direct electrical stimulation leads to behavioral responses ranging from sleep to rage (47). Stimulation of hypothalamic areas evokes a wide variety of autonomic responses involving smooth muscle, glands and heart (72). These effector organs are so intimately involved in emotional states that the hypothalamus has long been considered a center of emotional expression. Hypothalamic activation of the release of pituitary gonadotrophin, considered in detail in Chapter XXXIX by Harris in this *Handbook*, is facilitated by sex steroids of the same order of dosage as that which evokes mating behavior. This facilitation, by estrogen, of the release of pituitary ovulating hormone in response to direct electrical stimulation of the hypothalamus implies a hypothalamic or a hypophyseal site of estrogen action.

Among the lines of evidence implicating the hypothalamus in mating behavior is the recording of electroencephalographic (EEG) activity from hypothalamic sites during and after real or simulated copulation activity. In the estrous cat, as mentioned above, vaginal stimulation is followed by a dramatic behavioral after-reaction, lasting several minutes. Temporally related to this after-reaction are the EEG changes, illustrated in figure 7, bursts of high amplitude activity localized in the anterior lateral hypothalamus in and around the medial forebrain bundle but never in the posterior hypothalamus (69). These changes were observed only in estrous or estrogen-primed cats. If the after-reaction represents a behavioral expression of orgasm in the cat, the changes may signify EEG concomitants of this phenomenon; but orgasm is difficult to assess in animals (6).

In unanesthetized, unrestrained female rabbits with chronically implanted electrodes, Green (38)

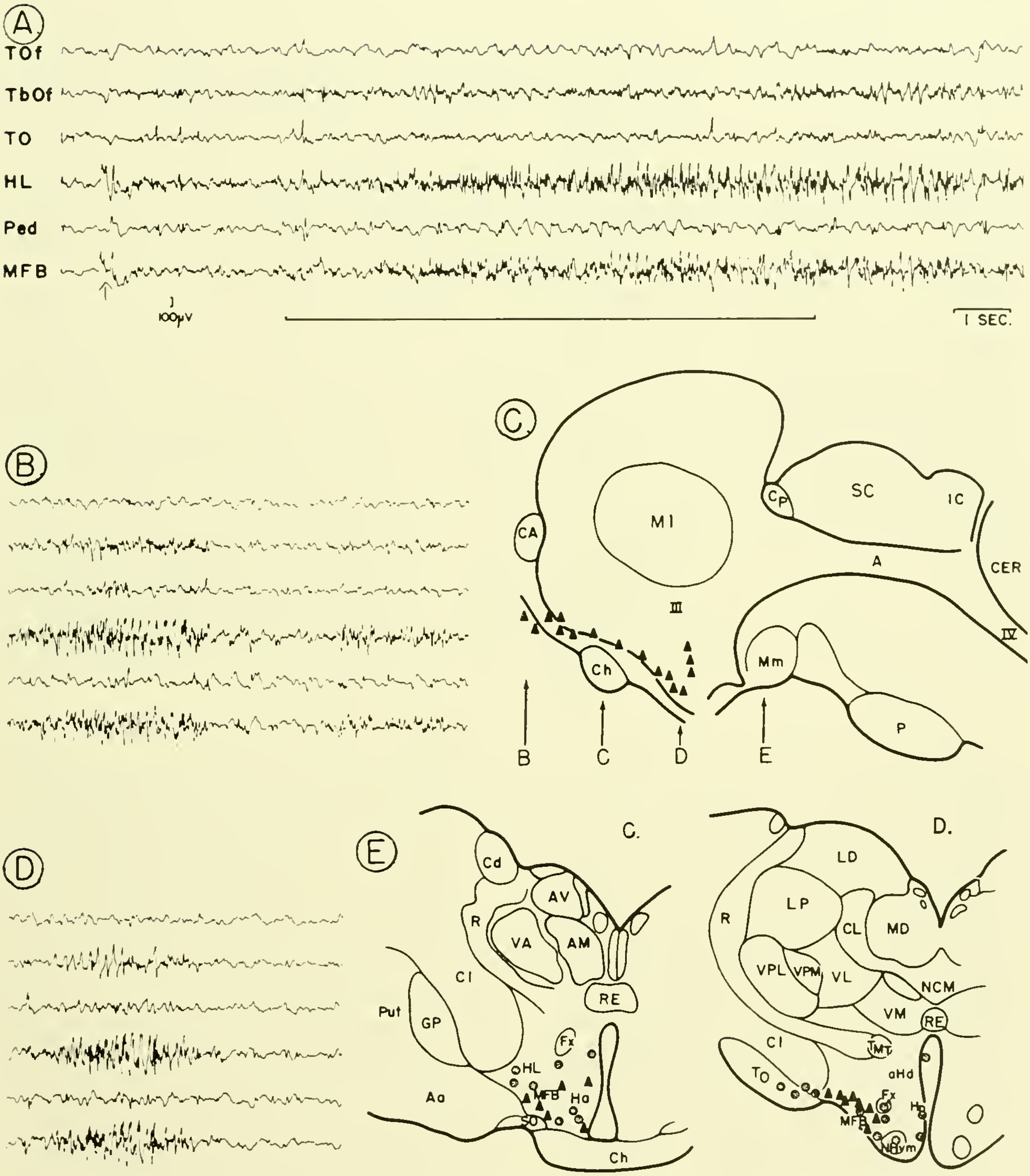

FIG. 7. Selected EEG tracings during vaginal stimulation (*A*) and 'after-reaction' (*B*, *D*) which lasted 3.3 min. in an estrous cat. Dramatic changes are seen in lateral hypothalamic (*HL*) and medial forebrain bundle (*MFB*) channels. *C* and *E* are, respectively, a sagittal reconstruction and two cross-sections of the cat brain stem showing areas from which altered electrical activity was recorded (*solid triangles*) and areas failing to show these changes (*stippled circles*). [Adapted from Porter *et al.* (69).]

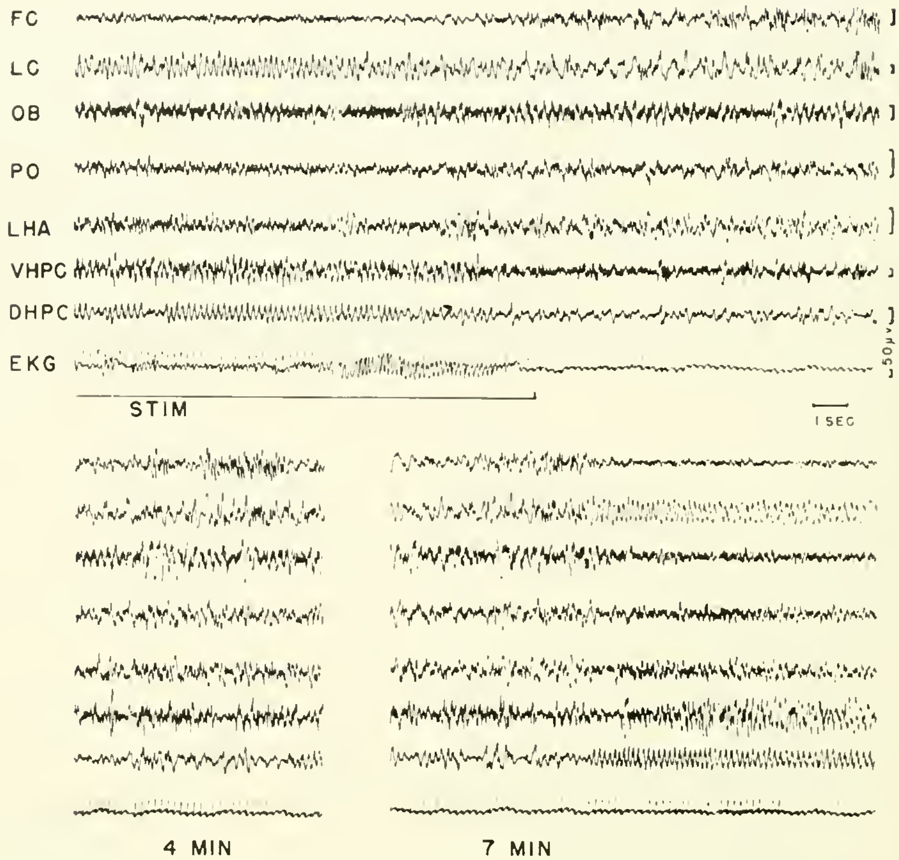

FIG. 8. EEG tracings during and after vaginal stimulation in an estrogen-treated estrous rabbit. The 'after-reaction' includes a sleep-like phase which here lasted 7 min., and a phase of 'pseudo-arousal' characterized by high amplitude slow waves (theta rhythm) in limbic cortical and hippocampal channels. Abbreviations: *FC*, *LC*, frontal and limbic cortex; *OB*, olfactory bulb; *PO*, preoptic area; *LHA*, lateral hypothalamic area, *VHPC* and *DHPC*, ventral and dorsal hippocampus; *EKG*, electrocardiogram. [From Sawyer & Kawakami, unpublished observations.]

has reported heightened EEG activity in the anterior hypothalamus during courtship and mating procedures. In similarly prepared rabbits, Kawakami and Sawyer have recently observed a generalized EEG 'after-reaction' which includes several minutes of a sleep-like record followed by an unusually aroused pattern. We have suggested that the latter is 'pseudo-arousal' since the rabbit remains quiescent while an extreme degree of EEG arousal is being registered. The response can also be evoked by vaginal stimulation in the estrogen-primed or estrogen-progesterone-treated rabbit (fig. 8). More interestingly, from the viewpoint of hypothalamic function, the 'after-reaction' EEG sequence can be initiated by low-frequency electrical stimulation, applied directly to the ventromedial region of the hypothalamus. Thresholds of this reaction will be mentioned below.

Further evidence for central sites of sex hormone action on behavior comes from the results of injecting hormone preparations directly into the cerebral ventricles or the brain tissue itself. Kent & Liberman (50) were able to induce psychic estrus in the castrate estrogen-primed hamster by injecting into the lateral ventricles of the brain a dose of progesterone too small to be effective via the systemic route. Harris (45) attempted to produce mating behavior in ovariectomized rabbits by injecting small amounts of stilbestrol into the hypothalamus—only to find that some of his untreated controls would mate without estrogen. He has more recently repeated this experiment with the female cat, and he reports that hypothalamically injected estrogen in doses too small to affect the uterus does indeed evoke psychic estrus (46). Fisher (30) reported the induction of sexual and maternal behavioral patterns in male rats by the injection of testosterone into the preoptic region.

An avenue of approach to the cerebral localization of sex drive is the self-stimulation technique of Olds & Milner (66). Rats with electrodes implanted in various regions of the brain are permitted to stimulate themselves ad libitum by pressing a bar in a Skinner box. Many areas are positively reinforcing; the electrical stimulus 'reward' activates repeated bar pressing at a rate dependent on the region and the strength

of the stimulus. Olds & Critchlow (personal communication) have recently found that the stimulus from certain electrodes, presumably hypothalamic, in castrate male rats is positively reinforcing only when exogenous testosterone is supplied. An excess of testosterone is inhibitory; but as the hormone level falls to within physiological limits, the bar pressing is resumed. An inverse relationship was observed between the responses to androgen and to hunger, implying differential centers for these two fundamental drives.

Rhinencephalic and Reticular Mechanisms

The rhinencephalon or limbic system has been associated with emotion ever since Papez proposed his now famous circuit in 1937. Papez (67) suggested that the circuitous sequence, involving the hippocampus, fornix, mammillary body, anterior thalamic nucleus, cingulate cortex and entorhinal cortex back to the hippocampus, was more likely associated with emotion than with olfaction. Gastaut (33) and Pribram & Kruger (70) have reviewed and clarified the interrelations of the limbic system, including the amygdala, septum and frontotemporal cortex. Gloor (34) and Green & Adey (39) have studied the detailed neuronal organization by electrophysiological methods. Green & Arduini (40), MacLean (60) and Adey *et al.* (1,2) have stressed functional connections between the limbic lobe and the ascending reticular activating center (63). According to Green & Arduini (40), afferent connections to the hippocampus include pathways from the reticular activating system, hypothalamus, preoptic region and septum while Adey *et al.* (1, 2) present evidence of reverse connections: fornix—hippocampus—entorhinal cortex—septum—stria medullaris—midbrain tegmentum. (See also Chapters LV, LVI and LVIII by Kaada, Green and Gloor in this *Handbook* which deal with these cortical areas.) Lindsley (58, 59) has suggested that the energizing aspects of emotion, motivation and drive may be supplied via the reticular activating system. From these anatomical and functional connections and interrelationships, the limbic and activating systems are in excellent positions to exert a collaborative influence on sexual behavior.

A dramatic demonstration of a rhinencephalic influence on a type of sexual behavior has been reported by MacLean (60). Local seizures in the cortex above the posterior cingulate gyrus in the male cat, induced by local chemical or electrical stimulation, were accompanied by penile erections and secretion. A similar tendency toward penile erection was evoked by electrical stimulation of the superior hippocampus in the rat. von Bechterew (93) may have stimulated one of these areas in his dog experiments in which electrical stimulation of the cortex produced erection and ejaculation.

Many locations within the rhinencephalon and midbrain have been found by Olds (65) to be positively reinforcing in the self-stimulation experiments described above. In these experiments the dependence of the rewarding nature of the stimulus on the intactness of the hypothalamus and upon hormone levels has yet to be ascertained.

Several studies have been made of the effects of hormones on the electroencephalograms (EEG) of rabbits and other species by Faure *et al.* (28, 29). These authors report differential changes in the EEG's of various rhinencephalic and hypothalamic loci within minutes after intramuscular injections of large doses of sex and adrenal steroids and placental gonadotrophins. The EEG changes occur so rapidly as to make one suspect nonspecific effects, and the records have not been correlated directly with reproductive behavior. However, further work with chronically implanted electrodes may prove these localized alterations in spontaneous electrical activity to be significant.

Within the first few hours after subcutaneous treatment with progesterone, the estrogen-primed rabbit is highly estrous in its mating behavior. During this period (fig. 9) Kawakami and Sawyer have found that its threshold of EEG arousal on direct electrical stimulation of the midbrain reticular formation is much reduced from its preprogesterone threshold (80). Vaginal stimulation or low-frequency stimulation of the ventromedial hypothalamus induces the EEG 'after-reaction' mentioned above, consisting of a sleep-like record followed by 'pseudo-arousal'—the latter is characterized by high amplitude theta or faster activity, especially in rhinencephalic leads: amygdala, hippocampus and limbic cortex (fig. 8). Twenty-four hours after progesterone treatment, the rabbit is usually anestrous. Its threshold of EEG arousal is markedly elevated (fig. 9) and vaginal or hypothalamic stimulation is not followed by the typical estrous EEG after-reaction. Hypothalamic stimulation, at higher voltage, may induce sleep spindles but not ordinarily the complete reaction with 'pseudo-arousal.' Estrus reappears with a return of the EEG arousal threshold to preprogesterone levels.

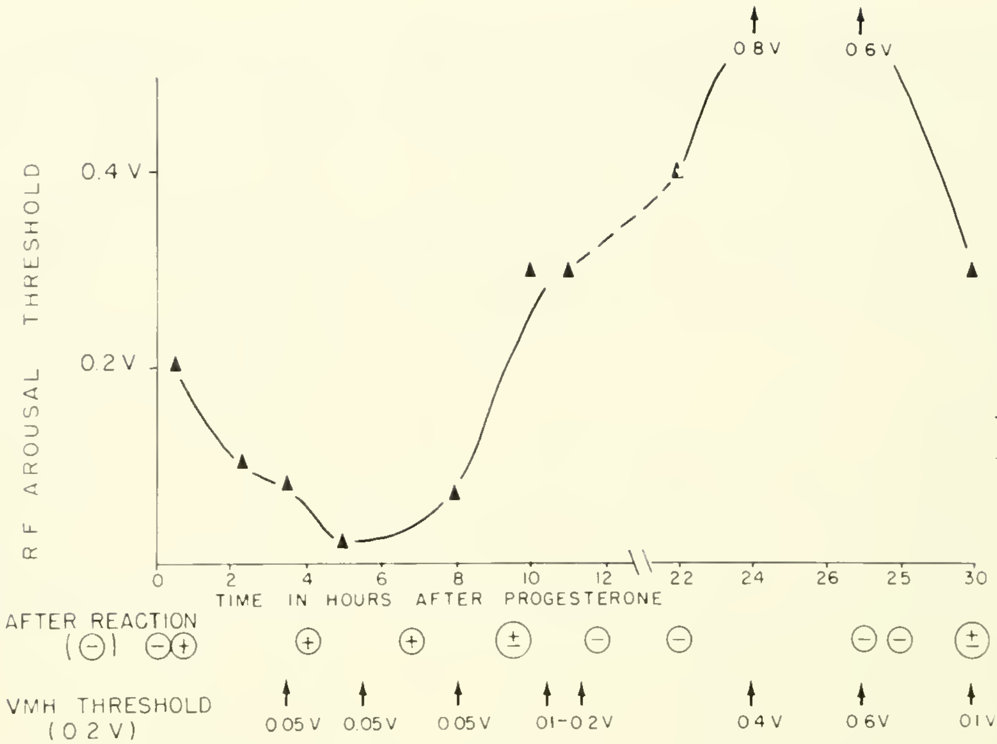

FIG. 9. Effects of progesterone on thresholds in an unanesthetized estrogen-primed castrate female rabbit. *RF*, reticular formation; *VMH*, ventromedial region of hypothalamus; 'after-reaction,' refers to EEG changes such as those seen in fig. 8, after vaginal stimulation. [From Sawyer (80).]

SUMMARY

Hormones may exert their effects at various levels within the nervous system to influence reproductive behavior. In general, subcortical centers appear to be more important than cortical. No level of integration below the hypothalamus can maintain more than a partial pattern of sexual behavior in either sex. Evidence from lesions, direct stimulation, direct application of hormones, electrical self-stimulation experiments and electrical recording data implicate the hypothalamus as a most important center of mating behavior. It is influenced especially by the rhinencephalon and the reticular activating system. In certain species the olfactory bulbs play a very important role, particularly in the male. The cortex, especially the medial, cingulate or retrosplenial area, appears to play an essential part in integrating reproductive activities which require initiative such as male mating, female maternal and maze-learning phenomena. Female mating behavior does not require the cerebral cortex in lower mammals, but it is especially dependent on hormone levels. Certain direct effects of hormone levels on thresholds within the nervous system have been demonstrated and correlated with mating behavior in the female rabbit. Neural correlates of behavioral after-reactions in mating have been recorded in the rabbit and cat.

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Central regulatory mechanisms—introduction[1]

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THE PHYSIOLOGIST who is faced with the problem of nervous integration hopes that eventually an illuminating synthesis will emerge from the experimental findings which he accumulates. Aware of the sterility of vitalistic evasions, he is a mechanist without illusions. By an act of deterministic faith, he accepts the theoretical possibility that all behavior may be explained in terms of the physicochemical activities of the neuronal network, the structure of which, infinitely complex though it be, appears to be decipherable.

Indeed the functioning of the bulbospinal segments of the vertebrate neuraxis is sufficiently regular to permit its description in terms of the dynamic factors brought to light by Sherrington and his school. The bodily movements resulting from the processes occurring in the integrating centers of the brain stem and even of the projection areas of the cortex can be interpreted as resulting from the activity of an input-output system. The presence of motor projections in many cortical areas, which until recently were considered to be exclusively sensory, provides anatomical evidence for the fundamental homology between cerebral mechanisms on the one hand and the reflex mechanisms of the lower neuraxis on the other. This homology is further illustrated by the ease with which reactions of the so-called motor areas can be evoked by afferent influences reaching them directly. Similarly corticocortical synaptic transmission, at least that involved in the callosal connections between cortical areas, notably the auditory areas, of the two hemispheres, shows a regularity of performance no less striking than that of elementary spinal reflexes. These experimental findings appear to justify the description of the fundamental architecture of the mammalian central nervous system as a progressive superimposition upon the segmental reflex arcs of circuits of increasing complexity, all of which originate in peripheral sensory mechanisms and end in motor or secretory effectors. The relatively unpredictable character of the processes occurring in the cerebral neuronal network, according to this view, results only from the participation of a colossal number of synaptically connected cells. The infinity of possible reaction patterns is made possible by the numerical immensity of the neurons available.

This confidence in the connectionist theory of central functioning must be tempered by confession of our ignorance of the nature of the supreme integrating principle whereby partial activities are fused and coordinated so as to produce the unity of the individual and the apparent spontaneity of his behavior. Nevertheless, we can take the position as Louis Lapicque did in giving the title *The Nervous Machine* to an essay that, with the reservation that such a coordinating principle may operate at the higher levels, the nervous system may be considered as an assembly of mechanisms.

A machine is made up of operational parts controlled by components providing automatic regulation. If we are to look on the nervous system as a machine, this distinction raises the semantic difficulty that the entire nervous system can be considered a regulatory appartus. All its activities tend to restore a dynamic equilibrium and to maintain its constancy—through its incessant re-establishment. In the regulatory processes information of extero-, intero- or proprioceptive origin evokes appropriate corrective responses by increasing some and decreasing other centrifugal impulse streams. The regulatory circuit may be considered to parallel the sensory and effector innervations and thus to modify their activity.

However, there apparently are also present in the

[1] The original was translated by Dr. Victor E. Hall.

nervous system of vertebrates, and doubtless of other higher metazoans, regulatory processes which deserve to be considered as of a second order. A part of the information which they employ does not stem directly from the peripheral sense organs. It arises from the very depths of the central gray matter and gives rise to influences which in turn affect their own output sequence. Clearly these closed-circuit regulatory activities can, when powerfully activated, produce effects which are readily apparent in modifications of posture and movements. However, in general these effects are so intimately integrated into the overall behavior of the animal that it is difficult to recognize their origins. The impossibility of detecting the participation of these mechanisms contrasts sharply with the seriousness of the disorders resulting from suppression of their activity. Thus there arises the difficulty of defining the precise nature of this regulatory function.

The functional connections which have been demonstrated experimentally between the bulbar respiratory center, the apneustic center and the pneumotaxic center in the anterior part of the pons constitute a striking example of nervous regulation operating by means of a closed central circuit. These three groups of neuron cell bodies, all of which lie in the brain-stem reticular formation, are almost certainly linked together functionally through an interchange of impulses, some transmitting information, others evoking excitation or inhibition regulating the duration and force of inspiration. This kind of nervous regulation of respiration, which may be called endogenous, is intimately associated with controlling reflexes but cannot be identified with them. Electrophysiological studies will doubtless eventually demonstrate the reality of this circulation of regulatory influences which is so far only a *vue de l'esprit*.

The hypothesis of thalamocortical reverberating circuits must be subject to similar reservations. Based on indirect experimental findings, not all of which are equally convincing, it still lacks definitive validation by direct oscillographic studies. We also need a clearer understanding of the functional significance of the exchange of information postulated to occur between the cerebral cortex and the various thalamic nuclei with which it is connected.

Despite the uncertainty in the interpretation of these concepts, we may assume that the central regulatory activity just considered characterizes the function of the cerebellum, the ascending reticular formation and its cephalic extension in the thalamus, and certain cortical and subcortical structures of the rhinencephalon *sensu lato*. This hypothesis has led to the discussion of these structures, otherwise so diverse, in the same part of the present *Handbook*.

The cerebellum, associated as it is with the great ascending and descending tracts of the neuraxis and reciprocally connected with the reticular formation and the telencephalon, is without doubt the organ most legitimately to be considered a regulator of central activities. It has long been known that its destruction does not abolish either any single simple reflex or any of the series of reflex chains by which the animal maintains itself erect and in equilibrium with respect to gravity. Cerebellar lesions on the contrary may cause a caricature-like exaggeration of these reflexes. Its electrical stimulation causes changes in postural tonus and in phasic contraction of large groups of muscles in patterns often deviating from the principle of reciprocal innervation. Moreover, the response to electrical stimulation of the anterior lobe is determined within narrow limits by the preexisting distribution of postural tonus and phasic movements of the muscles participating in the response. Everything happens as if cerebellar control always tends to re-establish an equilibrium. Finally it may be noted that the cerebellar cortex, the functioning of which is eminently tonic, shows a surprising autonomy in its spontaneous electrical activity. Thus the role of the cerebellopetal afferents appears to be limited to intensification and (less certainly at the moment) to inhibition of the autochthonous activity of this organ.

Nevertheless, in spite of the considerable mass of information which is available and which is critically reviewed in Brookhart's excellent chapter in this *Handbook*, the exact nature and *raison d'être* of cerebellar regulation still escape us. Impressed by the great number and variety of its afferent paths and by its reciprocal connections with all the projection areas of the cerebral cortex, Snider has suggested that the cerebellum may be "the great modulator of neurologic function." However seductive may be this view of an investigator who has contributed greatly to our knowledge of cerebellar connections, we hesitate to embrace it. There is one comparative anatomical fact which does not seem to have received attention and which appears to us quite significant. Two groups of teleosts, the cyprinoids and the mormyrides, both have a rich cutaneous innervation in the cephalic region. In the former, slowly-moving fish with mediocre motor capacity, the innumerable cephalic receptors are gustatory. In this group the cerebellum is rudimentary. In the latter, the cutaneous receptors, in-

nervated by a branch of the lateral line nerve, are adapted to perception of the currents produced by the periodic discharges of an electric organ of low power. This detecting apparatus is clearly one of the factors making possible the acrobatic agility of these fishes. In them the enormous cerebellum fills the cranial cavity with its exuberant proliferation One is tempted to see in this structural contrast a confirmation of the concept that cerebellar regulation is essentially concerned with the postural and phasic innervation of the skeletal musculature rather than with nervous functions in general.

The mesencephalic reticular formation responsible for arousal and the thalamic nuclei mediating its rostral influence qualify in every way for inclusion among the regulators of central activity. The original conception of Magoun and of Moruzzi was that this region produced a continuous stream of impulses which ascends to and energizes the cortical neuronal networks, and that the magnitude of this stream is determined simply by the intensity of afferent influences from the receptors. This concept now appears to be too simple if one accepts the views of Jasper and Fessard, which have been so well described by Jasper himself and by French in this *Handbook*. Even if the mesencephalothalamic mechanisms for arousal become recognized as of psychophysiological significance, it will not however be necessary to abandon the concept that they play a major role in the general regulation of cerebral activity, a regulation which cannot be other than the resultant of global functioning.

The reciprocal connections between the ascending reticular formation and the cortex pose problems which are still far from being solved. One of these is the intimate mechanism of cortical arousal by reticular influences. Another moot question is that of the participation of active inhibition in reticulocortical interactions. The only effects clearly revealed by experimental study of reticulocortical and corticoreticular influences are excitatory. The hypothesis based on these considerations proposes that cortical arousal regularly produces a corticifugal discharge back to the reticular neurons which intensifies and prolongs their activity, so in turn arousing them to further corticipetal discharge. The free play of this exchange of excitatory impulses, in the absence of an inhibitory autoregulation, might bring the organism dangerously close to a convulsive crisis. The demonstration of inhibitory mechanisms acting at the cortical or mesencephalic levels would confirm the view that the ascending reticular formation plays a homeostatic role in the overall functioning of the brain. It would further permit us to integrate into our interpretive synthesis the observations which led Hess to postulate a hypnogenic center exerting its effect by active inhibition.[2]

In the present state of our knowledge, interpretation of the functions of the rhinencephalic and nonolfactory cingulate structures is very difficult, a situation not dissimilar from that we meet in the case of the cerebellum. Experimental or pathological stimulation of these structures, particularly of the nuclei of the amygdaloid complex, results in striking changes in overt behavior and mental state both in animals and man. Even bilateral lesions of these structures, however, do not significantly impair the visceral or somatic activities which are clearly affected by stimulation. The rhinencephalon is thus not essential for the integration of the functions, the centers for which lie chiefly in the brain stem and hypothalamus. In still other regions, such as the anterior cingulate area, neither stimulation nor ablation yields clear results. The recent demonstration by Penfield and Milner and by A. E. Walker of the importance of the hippocampal-cingulate septum for the fixation of memory in man should dictate prudence in the evaluation of negative results from animal experiments.

If we set aside this unexpected suggestion that the hippocampus is critically related to the memory function, the impression which emerges from the mass of observations concerning the "second system of the rhinencephalon" (as Pribram & Krüger call it) is that its various constituent structures have, in the course of the phylogenetic evolution of the vertebrates, acquired the role of modulators of nervous activities integrated in the more primitive subcortical regions in which lie the nervous mechanisms for fundamental instincts. This role of modulation of intensity would account for their importance in the orientation of behavioral patterns and in the control of emotional tension. The description and analysis of these subtle influences must take full account of the nuances of psychological dialectics. The writers of the pertinent chapters in this *Handbook* have succeeded perfectly in this task.

[2] Since these lines were written, the existence of such an inhibitory mechanism in the pontine reticular formation has been demonstrated by Moruzzi and his associates.

The cerebellum[1]

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CHAPTER CONTENTS

HISTORICAL BACKGROUND

THE STORY OF THE GROWTH of knowledge of the physiology of the cerebellum recapitulates the story of the growth of almost all branches of human knowledge. Opinions originally founded on pure speculation have been supplanted by opinions based upon

[1] Prepared during the tenure of a grant under the Fulbright Act.

[2] The author wishes to express his sincere gratitude to Dr. G. Moruzzi and Dr. R. S. Dow for their generous permission to study the prepublication manuscript of their major and exhaustive monograph on the physiology and pathology of the cerebellum which appeared in 1957.

observation. Long before the dawn of the scientific era, the cerebellum was recognized as a special portion of the central nervous system. However, from the time of Galen through the writings of Thomas Willis, opinion concerning cerebellar functions was based entirely upon speculations, framed in what we now consider to be meaningless terminology and based on the confused concepts of neural function in vogue at any particular time. Nevertheless, Willis' speculative suggestions (364) that the cerebellum controlled such functions as the heart beat, respiration and other vegetative functions, led eventually to experimental investigations which, although they refuted his suggestions, have laid the foundations for our present concepts of cerebellar function. Discussions of this period in the development of cerebellar physiology may be found in Neuberger (253) and Rawson (278).

The true nature of cerebellar function began to emerge with the first crude attempts to describe the alterations in behavior following the removal of the cerebellum from live animals. Through the work of Duverney (115), von Haller (352), Rolando (280) and Flourens (124), the broad outlines of cerebellar influence over the control of motor activities of the central nervous system were soon laid down. Through the subsequent years, the refinements of surgical skill in the preparation of experimental ablations, increasing sophistication on the part of clinical observers and the development of new techniques of inquiry have contributed accuracy and precision to the descriptions of cerebellar dysfunctions. The beginnings of true understanding, however, have only begun to develop on the background of the anatomical understanding which has been furnished by the work of comparative and experimental anatomists guided so importantly by Larsell and the workers of the Norwegian school.

Throughout the earlier portion of the experimental period, several unrecognized difficulties were encountered by investigators which added measurably to confusion and differences of opinion. As is the case with the cerebral cortex, the cerebellum has undergone extensive phylogenetic alteration in structure and function. The species differences resulting from these alterations were not immediately recognizable. The earlier experimental work also suffered from lack of histological controls of experimental procedures. The existence of intracerebellar decussations, the proximity of nuclear and cortical structures, plus the juxtaposition of the cerebellum and important motor control systems of the brain stem, make histological controls mandatory in any experimental study of the cerebellum. Much of the earlier experimental work is impossible to interpret with any degree of assurance because of the absence of such controls. And finally, the ability of experimental animals to compensate for experimentally-produced cerebellar deficits introduces an important time factor into experimental studies involving chronic cerebellar lesions which was not taken into consideration in much of the work of the nineteenth and early twentieth centuries. The student of the original literature on cerebellar physiology should bear these points in mind in evaluating the reports which he reads.

ANATOMICAL ORIENTATION

It is unnecessary here to consider the anatomical relations of the cerebellum in detail. For exhaustive treatment of this important subject the reader is referred to Larsell (181) and to Jansen & Brodal (169).

Gross Morphology

The purely functional aspects of the cerebellum have constituted the primary objective of many studies. On the other hand, many investigators have initiated cerebellar studies with the objective of defining somatotopic relationships within the cerebellum. Luciani (188–190) early emphasized the conclusion that there was a lack of somatotopic organization within the cerebellum with the exception of the relation of one side of the cerebellum with the ipsilateral side of the body. Nevertheless, Bolk's comparative anatomical studies (27), appearing at about the same time that information concerning the somatotopic organization of the cerebral motor cortex was being revealed, gave great impetus to attempts to demonstrate a similar organization of the efferent functions of the cerebellum. Studies of the more detailed anatomy of the cerebellum soon led Edinger (116) and Comolli (77) to suggest another variety of organization. According to this concept, the paleocerebellum comprising the vermis and flocculus was phylogenetically older and was concerned primarily with the regulation of tonus; the neocerebellum, on the other hand, consisting of the cerebellar hemispheres, was primarily concerned with cerebral relationships. Ingvar (164, 165) added to this concept by proposing that the paleocerebellum

received largely vestibular and spinal afferents whereas the neocerebellum received afferents activated from the cerebral cortex. The physiological justification for the distinction between the paleo- and neo-portions of the cerebellum was first offered by Bremer (36). Further studies of comparative and developmental anatomy have led Herrick (157) and Larsell (180) to reinforce this distinction. More recent anatomical studies (169), and the evidence which will be reviewed, indicate that this partition of functional relationships is too rigid and that cerebrocerebral relations must be mediated in part by the more anterior portions of the paleocerebellum.

Undoubtedly the most universally applicable and useful description of the gross morphology of the cerebellum is that which has grown out of Larsell's comparative and embryological studies (180). The basic subdivision into a flocculonodular lobe separated from a corpus cerebelli by a posterolateral fissure is applicable to all species studied. Larsell further subdivides the corpus cerebelli into an anterior and a posterior lobe. The further subdivision of the corpus cerebelli into lobules has been accomplished in the past through the use of terms which were not universally applicable. In what is to follow, an attempt is made to use current terminology along with the numerical designation recommended by Larsell (181). Figure 1 is an attempt to represent the morphology of the cerebellum. The additional division of the cerebellum into sagittal divisions consisting of a vermis, and an intermediate and lateral portion of each hemisphere seems indicated by both anatomical and physiological evidence which will be discussed later.

The functional importance of this gross morphological subdivision of the cerebellum resides in two facts. The flocculonodular lobe is the only portion of the cerebellum which has direct two-way connections with the vestibular system. The phylogenetic development of the cerebral cortex is coupled with the phylogenetic development of the lateral portions of the cerebellar hemispheres.

Cortex

The outstanding histological characteristic of the large expanse of highly infolded cerebellar cortex is its uniformity in all parts of the cerebellum. This cortex is divisible histologically into three layers: a superficial molecular layer, at the bottom of which is found the row of Purkinje cells; and a deep granular layer overlying the white matter. Neurons are relatively sparsely scattered in the superficial portion of the molecular layer, the bulk of the volume being comprised of the tremendous dendritic expansions of the Purkinje cells enveloped with climbing fibers, the ascending and bifurcating axons of the granule cells of the third layer, and the axons and dendrites of the star cells and basket cells of the molecular layer. At the base of the molecular layer the row of Purkinje cells is composed of the large globose somata of these cells arranged almost in contact with each other, separated by the basketwork of axonal terminations derived from the basket cells of the molecular layer. The granular layer is composed chiefly of the densely packed bodies of the granule cells, their complex dendritic expansions which intertwine with the terminals of the incoming mossy fibers, Golgi type II cells and the incoming and outgoing fibers of passage.

The impulses to the cerebellar cortex are delivered over the mossy fibers from such diverse sources as the spinal cord, the cerebral cortex via the pontine nuclei, the reticular nuclei of the tegmentum and medulla, and the vestibular system (cf. 169). The origin of the impulses delivered to the cortex by the climbing fibers still remains in doubt, the suggestion that they originate as recurrent collaterals of axons of intracerebellar nuclei (63) not being acceptable to all (292).

Efferent impulses from the cerebellar cortex are discharged entirely over the axons of the Purkinje cells, there being no other known axon which leaves the cortex to enter the white matter.

Nuclei

The cell bodies of the cerebellar nuclei constitute the end station of the vast majority of Purkinje cell axons. In step with, and as a reflection of, the phyletic development of the cerebellum, the cerebellar nuclei undergo variations from species to species. In the mammal, the medial nuclear group, the fastigial nucleus, is the oldest from the phylogenetic point of view. Its extracerebellar input is dominated by the vestibular inflow and its output is principally directed to bulbar areas. The intermediate group is homologous with the interpositus in lower mammals and with the nuclei globosus and emboliformis in primates. The lateral group is homologous with the dentate nucleus of the primate.

The corticonuclear relations of the cerebellar nuclei have been satisfactorily clarified for the cat (167), rabbit and monkey (168) by Jansen & Brodal.

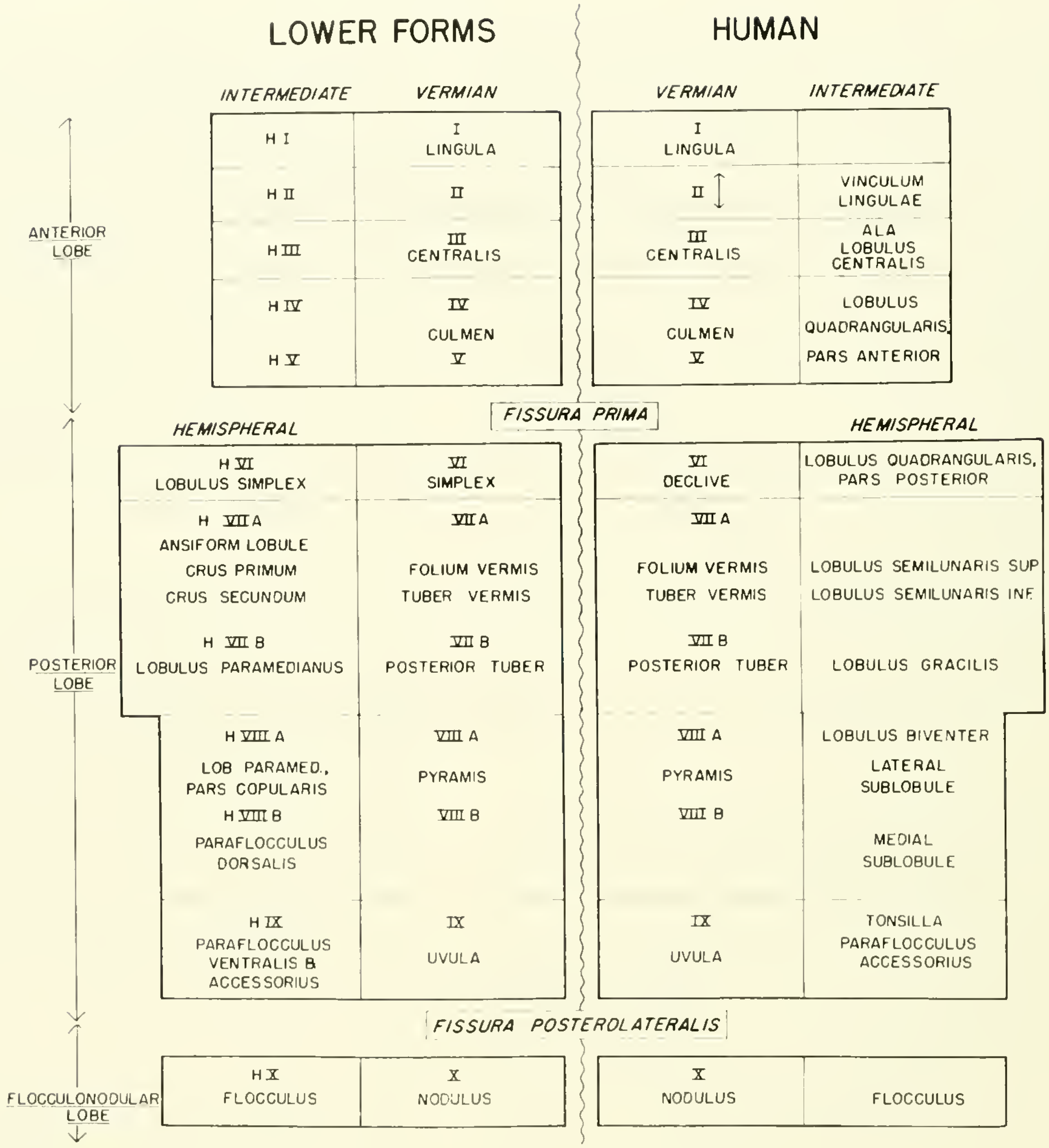

FIG. 1. Highly schematized representation of the gross morphology of the mammalian cerebellum. The figure is intended to convey the relative positions of the various lobes, lobules and sublobules along with their names. The *left half of the figure* is labeled according to the names applicable to mammals frequently used in experimental studies. The *right half* is labeled with names applicable to the human cerebellum. The homologies are indicated by the names appearing on the same *horizontal line*. The *vertical lines* indicate the separations of the anterior lobe into vermian and intermediate portions, and the posterior lobe into vermian and hemispheral portions. The *Roman numerals* indicate the system of nomenclature which has been proposed by Larsell (182) and which is based upon the relations of the primary medullary rays of the cerebellar white matter. Hemispheral and intermediate portions of each subdivision are indicated by the *prefixed H*. There is considerable unresolved confusion in the literature regarding the proper designation of the lingula in the subhuman mammals. In the human lobules I and II vary considerably in size. When lobule I is much reduced in size, the correspondingly larger lobule II becomes the sublobulus centralis anterior of Ziehen and has often been regarded as part of the centralis. [The original basis for this figure was derived from the table presented in Jansen & Brodal (169). The modifications from the original have been accomplished with the generous advice and assistance of Dr. O. Larsell.]

The medial nuclei receive cortical projections from the vermian portions of both anterior and posterior lobes. Cortical projections from the intermediate portion of the anterior lobe and hemisphere, from the paramedian lobule, and to a certain extent from the paraflocculus terminate in the intermediate nuclear group. The lateral nuclear group receives its corticonuclear fibers from the lateral portions of the hemisphere and from the paraflocculus. This cortico-nuclear projection is strictly ipsilateral. The anterior portions of the cerebellum project into the anterior portions of each of the nuclear groups, and posterior onto the posterior, in a perfectly regular pattern. This systematic relationship between the cortex and the nuclei is the anatomical basis for the sagittal subdivisions of the cerebellum mentioned earlier.

The outflow from the various cerebellar nuclei has been a difficult and confusing problem for many years. Perhaps the most clear-cut description of the relationships is afforded by Jansen & Brodal (169). Since a thorough appreciation of these outflow pathways is essential to an interpretation of many physiological investigations, no attempt will be made to outline the facts here. Rather the reader is referred to the more complete discussion.

In considering cerebellar influences upon other portions of the brain, it is essential to bear in mind that some Purkinje cell axons from all parts of the vermis and from the flocculus leave the cerebellum without interruption (167, 168). These axons terminate primarily in the vestibular nuclei ipsilaterally to their origin.

Extracerebellar Relations

The cerebellum is related to the remainder of the nervous system by fibers coursing through the three cerebellar peduncles. The principal inflow to the cerebellum from the medulla and the spinal cord occurs through the inferior cerebellar peduncle. Through this structure come impulses from spinal cord nuclei, from the inferior olivary nucleus, from the dorsal column nuclei, from the vestibular nuclei and from the reticular nuclei of the medulla. Outflow paths through the inferior peduncle relate the cerebellar cortex and nuclei to the vestibular nuclei, the inferior olivary nuclei and the reticular nuclei. The middle cerebellar peduncle is composed almost entirely of fibers originating in the nuclei of the pons. Through this pathway the cerebellar cortex, principally of the hemispheres, the vermis and the paraflocculus, is subjected to the influence of most portions of the neocortex of the cerebral hemispheres. The superior cerebellar peduncle contains fibers of the ventral spinocerebellar tract and some fibers from the tectum and tegmentum. Its great bulk, however, is made up of axons from all of the cerebellar nuclei destined for the thalamus, the red nucleus, the motor nuclei of the brain stem, and the reticular nuclei of the mesencephalic, pontine and medullary tegmentum.

CHARACTERISTICS OF CEREBELLAR ACTIVITY

The characteristics of activity of cerebellar neurons, like those of other portions of the central nervous system, have been studied rather intensively only during the last 15 years. Very early attempts to apply electrophysiological techniques to this problem were made by Beck & Bikeles (19, 20) and Camis (57) utilizing inadequate recording techniques. More recently, advances in electrophysiological techniques have made possible the acquisition of information important from both the physiological and the anatomical points of view.

Spontaneous Cerebellar Activity

ELECTRICAL ACTIVITY OF CEREBELLAR SURFACE. The first recognition of the characteristic electrical activity of the cerebellar cortex was made by Adrian in 1935 (1). Since that time it has been found that the cerebellar cortices of the fish (342), the amphibian (21), the reptile (91) and the bird (54, 55, 360) display a pattern of activity essentially similar to that seen in mammals, a datum which permits the inference that this basic activity is dependent upon some intracortical organization of neurons which is peculiar to this anatomically uniform cortex. The typical electrocorticogram from the surface of the cerebellum consists of roughly rhythmic potential oscillations of frequencies in the range of 150 to 250 per sec. The voltages recorded may vary from .020 to .120 mv, depending apparently upon the general condition of the preparation (240). Dow (106) soon confirmed Adrian's observations and added further information of importance. This rhythmic surface activity was shown to originate within the cerebellar cortex, to be correlated with evidences of cerebellar influences on extracerebellar structures, and to be exceptionally vulnerable to hypotension and easily depressed by anesthetics, anoxia and ischemia. The existence of the fast cerebellar rhythm has been

confirmed by numerous investigators (81, 143, 320, 363). Furthermore, the origin of the rhythm has been localized to the Purkinje cell-granular layer and has been differentiated from the single action potentials of cerebellar units (52), and the rhythm has been shown to persist in spite of neural isolation of the cerebellar cortex (89). In addition to the fast (150 to 250 per sec.) rhythm which is distributed over the entire surface of the cerebellum, slower potential oscillations have also been observed in both anesthetized and decerebrate animals. Potential oscillations at 8 to 12 per sec. have been recorded primarily from the hemispheral portions of the cerebellum of animals under barbiturate anesthesia (81, 143, 320, 328, 329, 342, 363). Since these low frequency rhythms disappear upon transection of the mesencephalon, it is concluded that they are due to the arrival of corticofugal discharges from the cerebrum. In decerebrate animals, prepared with extreme care and maintained in the best condition, an additional variety of slow potential oscillations of approximately 20 msec. in duration is observed at the cortical surface (214, 239, 240). These latter waves appear to differ in origin from the fast rhythm, but their source remains uncertain.

At the low end of the frequency spectrum, it has recently been observed that sustained d.c. shifts of potential occur at the cerebellar surface as a result of peripheral nerve stimulation (5). These negative shifts endure for 1 to 3 sec. after single shocks to peripheral nerve, are enhanced by local strychnine and depressed by local pentobarbital. Their significance remains obscure. The phenomenon may be the same as that recorded many years ago by Beck & Bikeles (19, 20) using galvanometric recording.

ACTIVITY PATTERNS IN CEREBELLAR NEURONS. Since the introduction of techniques permitting the observation of activity in single neurons, information about cerebellar neurons has grown less rapidly than one might have expected. This is in part due to the technical difficulties involved in penetrating and holding single neurons in the pulsating cerebellum, and in part due to sensitivity of the cerebellar cortex to depressing influences mentioned above.

The first attempts at examining single unit activity were only partially successful in that the identity of the units recorded could not be surely established. Nevertheless, Brookhart *et al.* (51), utilizing small wires inserted into the vicinity of Purkinje cells, recorded extracellular action potentials which they believed to originate from Purkinje cells. In decerebrate animals, these units showed a rather high level of spontaneous activity, discharging at frequencies ranging over wide limits, the majority falling into the range of 70 to 80 per sec. This spontaneous activity was characterized by random intermittency, discharges occurring in groups separated by silent intervals. The factors controlling the resting discharge and the intermittency of firing could not be elucidated, although similar behavior was recorded from units in surgically isolated areas of the cortex. The units could be caused to fire and could be augmented or inhibited in their activity by impulses originating in the cerebral cortex or in peripheral receptors. Intense afferent activity, or locally applied strychnine, initiated convulsive discharges which appeared to be self-terminating at frequencies of 400 to 500 per sec. By means of the same technique, it was later (52) shown that both the unit and wave activity was localized to the Purkinje-granule layer, and that the spike and wave activity were differentially sensitive to ischemia and anesthetics. The cerebellar units are also responsive to polarization with constant currents according to the rule that current flow oriented in the dendritoaxonal axis of the Purkinje cells nearest the electrode tip increased discharge; current flowing in the axodendritic direction reduces discharge; and current flowing parallel to or at right angles to the dendritic tree has no influence on discharge (49, 50).

While it remains true that information from intracellular recordings continues difficult to obtain, enough observations of this type have appeared to establish the fact that Purkinje cells are, in some respects, like other neurons and, in other respects, show peculiar properties (54, 55, 138, 139, 343). Observations of the most importance have been made by Granit & Phillips. These investigators have recorded both intra- and extracellularly from neurons which several lines of evidence identify as Purkinje cells. The general pattern of activity was the same as that observed previously with extracellular wire electrodes (51). They find the discharge of the cell to be preceded by a prepotential which originates at some distance from the recording site. Enough intracellular recordings have been obtained to indicate that the prepotential is generated by a mechanism different from the action potential and that cessation of cell firing may be accompanied by hyperpolarization. These facts align the Purkinje cell with spinal cord cells (82), cells of the cerebral cortex (260) and the peripheral stretch receptor of the crayfish (176). On the other hand, cessation of activity in Purkinje

cells may also be accompanied or produced by *a*) excessive depolarization following intense activation and by *b*) a transient depolarization lasting 15 to 30 msec. and having the character of an organized control mechanism. Direct stimulation of cerebellar neurons (139) was found to be possible with very low voltage positive pulses applied near superficial units (see also 49, 50). With single and repetitive stimulation, the Purkinje cells could be excited, inhibited, triggered, driven and thrown into higher levels of spontaneous activity.

Single neurons of the fastigial nuclei have also been observed in spontaneous activity (271). It has been possible to alter the activity of these neurons by vermal polarization, labyrinthine polarization and sensory nerve stimulation.

Cerebellar Activity as Altered by Surface Stimulation

SINGLE SHOCKS. The effects of surface polarization of the cerebellum on unit activity have already been alluded to (49, 50). This technique has been utilized to study cerebellar influences on units of the reticular formation (130, 213, 293, 350).

Dow (109) has recorded surface negative responses to single shocks with evidence that these are slowly conducted (0.5 m per sec.) through fibers of the molecular layer. Dow also presents evidence that the conducted activity may cause Purkinje cell discharge. This observation has recently been repeated (139).

REPETITIVE STIMULATION. Repetitive stimulation of the surface of the cerebellum is followed by a variable sequence of events depending, apparently, upon the intensity and duration of the stimulus train. At the site of stimulation, there follows a period of electrical silence if the period of stimulation has been short, or a period of convulsive after-discharge, represented by an increase in amplitude and frequency of background activity if the stimuli are more intense or the train is slightly prolonged (1, 106, 214). Following the convulsive pattern, there ensues a period of reduced activity or of electrical silence, after which the normal electrogram once more appears. This sequence of electrical changes has been shown to be accompanied by alterations of spinal cord function, and therefore must be related to alterations in cerebellar neuronal discharge (106).

An electrical silence following intense (up to 200 v., 40 ma peak, 1 msec. pulses at 280 per sec.) prolonged (30 sec.) stimulation of the cerebellum or brain stem has been termed 'cerebellar electronarcosis' and has been attributed to inhibitory reverberating circuits between the mesencephalon and cerebellar cortex (142, 144–147, 204). However, it has been pointed out that with stimulation parameters of these values, the brain stem is directly activated by spread of stimulating current and that the stimuli exceed the thresholds for physiological responses by 5 to 50 times (7, 239, 292). It has also been demonstrated that when stimuli which are threshold for the production of convulsive after-discharge are prolonged for 20 to 30 sec., electrical silence supervenes—an effect which is independent of the level of mesencephalic transection (214). It thus seems unnecessary to postulate inhibitory mesencephalocerebellar relations when evidences of simple exhaustion are adequate to account for the observations.

Cerebellar Activity as Altered by Cerebellopetal Impulses

FORM OF EVOKED POTENTIAL. Since the first observations (131) and the subsequent studies by Snider & Stowell (311) and by Adrian (2) of potentials at the surface of the cerebellum produced by sensory stimulation, it has been noted that the form of the evoked potential is essentially the same whatever the origin of the causative impulses. From this it may be inferred either that *a*) all of the incoming activity thus far tested arrives at the cortex over mossy fibers (see 169) or that *b*) mossy and climbing fibers both produce a similar sequence of sources and sinks by postsynaptic activation. The latter inference seems unwarranted on purely anatomical grounds.

The arrival of a synchronized volley of impulses in corticipetal fibers produces an initially positive wave form of 0.1 to 0.3 mv and a duration of 20 to 30 msec. This is succeeded by a more leisurely, usually smaller, negative wave which may occupy 30 to 40 msec. Such responses are highly localized in anesthetized or depressed animals when the initiating stimuli are confined to a small population of afferents. This localized characteristic has led to the widespread use of the evoked response in electroanatomical studies which will be discussed later. In unanesthetized preparations, the evoked response is frequently succeeded by a period during which the spontaneous rhythm of the cortex is increased in frequency and amplitude (2, 38, 39). This altered rhythm may resemble convulsive activity, but it is promptly blocked by the elicitation of a second evoked response.

The genesis of the surface sign of evoked response has been studied using simultaneous leads from the

surface and depth of the cortex (28, 38–40, 42, 44, 294). The negative component of the response is more labile, more subject to depressing influences, may be augmented by local strychnine and shows temporal summation as a result of properly-timed paired volleys. From these considerations, and from the inversions of potential sign which occur at a penetrating electrode (44, 215, 294), it appears justifiable to conclude that the positive phase of the evoked response develops from postsynaptic activity in the granular layer of the cortex whereas the negative phase is related to the efferent discharge of Purkinje cells.

SENSORY INPUT. The electrical activity of the cerebellum is capable of being altered by impulses originating in a wide variety of sensory nerves. Before dealing with the problems of localization on the cerebellar cortex, it seems pertinent to consider the nature of the afferent activity initiated in these studies and the pathways of transmission involved.

In those studies in which natural sensory stimuli were used to activate receptors, there can be little doubt about the nature and distribution of the afferent fibers. It has been found that afferent activity initiated in muscles, tendons and joints is delivered to the cerebellar cortex (2, 110, 140, 177–179). This is in keeping with the long-recognized importance of the cerebellum in relation to postural control. The discovery that the stimulation of cutaneous receptors (2, 75, 110, 131, 303, 311, 312) and even auditory and visual receptors (28, 41, 117, 128, 129, 131, 311, 312, 319) could also activate the cerebellar cortex was unexpected since it had not been predicted on either anatomical or physiological grounds.

The technique of evocation of cerebellar responses by electrical stimulation of sensory nerves introduces complications which have been of concern to some investigators. With artificial stimulation, it has been noted that the evoked response is dependent to a certain degree upon the nature of the stimulated afferents and the conduction pathway. It has been reported that the surface response is divisible into three distinct portions having different latencies (140, 179). It is generally agreed that the initial component of shortest latency results from the stimulation of Group I afferents and that the impulses course through the dorsal spinocerebellar tract (61, 107, 140, 178, 216, 248). There is a lack of clarity in the relationships between the later components of the response reported by various investigators, particularly with respect to their latency and to their utility for localizing purposes. The component of intermediate latency has been ascribed to a response of neurons of the cerebellar cortex (140) and to more slowly conducted afferent activity (178, 248). A still later component has been considered to originate from impulses in more slowly conducting cutaneous afferents (140, 178) and in slowly conducting afferents in muscle nerves (216, 217, 248).

The problem of the conduction pathway utilized within the central nervous system has been attacked principally with the technique of partial cord transection. Because of the possibility of sparing a few effective fibers, this approach presents problems which are not completely avoided by the technique of recording from the ascending fiber systems. In the opinion of some investigators, both the dorsal and ventral spinocerebellar tracts conduct impulses of both cutaneous and proprioceptive origin, and convergence from the two sources upon single elements of the tract occurs (61, 140, 148, 217). At the level of the superior cerebellar peduncle (61) ventral spinocerebellar tract impulses may arrive over both crossed and uncrossed pathways, and evidence of additional crossing within the brain stem or cerebellum has been obtained as predicted by anatomical studies (48). On the other hand, Oscarsson (256) reports that the ventral spinocerebellar tract, at spinal cord and peduncular levels, is activated solely from contralateral muscle nerve stimulation in which the volley includes Group Ib afferents. Oscarsson's studies also led him to the conclusion that the dorsal spinocerebellar tract is largely uncrossed and may be activated by both Group Ia and Ib afferents.

The dorsal column system has been shown to be activated by impulses originating in skin, muscle and joint nerves (64, 216, 218). The ventral quadrant of the spinal cord also furnishes an important pathway to the cerebellum in the form of the crossed spino-olivary and uncrossed spinoreticular fibers (26, 148, 217) capable of being activated by both cutaneous and proprioceptive stimulation. In these systems, too, further crossing has been shown functionally and anatomically (48) to occur at the upper end of the pathway.

The degree of localization of cerebellar responses evoked by natural or by artificial stimulation of sensory nerves has not been uniform in all studies of this subject. In Dow's early studies on decerebrate cats (107), sciatic, saphenous, median and ulnar stimulation gave rise to responses which appeared bilaterally over the anterior lobe (I–V, H I–H V), simplex (VI, H VI), pyramis (VIII A, VIII B) and

paramedianus (H VII B, H VIII A). Similar results were obtained in the lightly pentobarbitalized rat (110). This generalized distribution of response was not reported by later investigators working largely with animals under the influence of barbiturate anesthesia. These differences have been made the subject of a special study by Combs (75). Utilizing both natural and artificial stimuli, Combs found that responses were diffusely distributed over the anterior lobe (I–V, H I–H V) and simplex (VI and H VI) in the decerebrate unanesthetized animal. The diffuse responses were not the result of intracortical spread because they appeared with relatively uniform latency over the entire lobe and furthermore survived rather deep and extensive ablations of those portions of the cortex from which others had recorded localized responses. Following the administration of pentobarbital to the same animals, the responsive zone shrank to a small ipsilateral region of the intermediate portion of the anterior lobe, the exact location of which was characteristic of the site of stimulation. These observations were tentatively explained by postulating the existence of two afferent systems differentially susceptible to pentobarbital, an hypothesis which has been supported by additional observations (76). The localized response in the anesthetized animal was shown to be independent of the dorsal and ventral spinocerebellar tracts, the spino-olivocerebellar system and the external cuneate nuclei, but disappeared upon destruction of the lateral reticular nucleus. It would thus appear that impulses of somesthetic origin are delivered diffusely to most of the anterior lobe and simplex and to the paramedian lobes by one or more ascending systems, whereas other ascending systems deliver only to restricted foci within this larger responsive area. It would appear possible that examples of interaction of evoked responses at one point on the cerebellum from widely separate afferent sources (28, 41, 216, 217) may have been dependent upon the utilization of experimental preparations showing the generalized responses described by Combs (75).

The localized responses from hind limb regions, when studied in anesthetized animals, appear ipsilaterally in the culmen (IV, V, H IV, H V), from fore limb regions in the culmen (IV, V, H IV, H V) and from face areas in the simplex (VI, H VI) (2, 312). In addition to these responses from the anterior lobe, localized responses may also be recorded from the paramedian lobes (H VII B, H VIII A) bilaterally with considerable overlapping of foreleg, hind leg and face areas (312). Occasionally, responses from somatic stimulation are recorded from the ansiform lobules (H VII A) (312). The distribution of activity from deep and superficial sources shows no detectable differences (216, 217).

From vestibular sources also, evoked potentials appear in these portions of the cerebellum known anatomically to be closely related to vestibular function. Thus, single shocks applied to vestibular structures produce evoked potentials in the flocculonodular lobe, the uvula (IX), lingula (I) and lobulus centralis (III) as well as in the fastigial nuclei (107).

Natural stimulation of auditory receptors, as well as natural and artificial stimulation of visual input, has produced responses in the simplex (VI, H VI) and in the folium and tuber vermis (VII A, VII B) (312). Visual responses have also been recorded from the ansiform lobule (H VII A) and are more easily found when the animal is anesthetized with chloralose (312). This characteristic has resulted in the suggestion that the ansiform lobule responses are abnormal in the sense that they depend upon the convulsant properties of chloralose (128, 129). Evidence as to the physiological nature of these responses and their independence of chloralose has recently been presented (117).

As a result of stimulation of vagus nerve fibers (95) and olfactory bulbs (162), responses have been recorded from the same zones which are activated by tactile impulses from the face. Single shock stimulation of the splanchnic nerve with currents strong enough to activate thin myelinated fibers of the delta category produces evoked responses in various portions of the vermis (IV, V, VI, VII A, VII B) and from the paramedian lobules (H VII B, H VIII A) (362).

IMPULSES FROM CEREBRAL CORTEX. Allusion has already been made to the fact that spontaneous cerebral rhythms may have an influence upon the activity of the cerebellar cortex. As might be expected, activity initiated by artificial stimulation of the cerebral cortex may also evoke responses from the cerebellum. Such responses have been valuable in establishing the existence of functional pathways between these two portions of the central nervous system in support of and in extension of the more purely anatomical descriptions.

Starting from the observations of Curtis in 1940 (93), subsequent investigations have supplied confirmation and refinement. In the anesthetized cat, electrical (93, 108) and chemical stimulation of many areas of the cerebral cortex elicits rather

widespread bilateral responses (stronger contralaterally) from the cerebellar hemispheres and the more posterior portions of the anterior lobes. In the monkey, Dow (108) and Adrian (2) have reported somewhat finer degrees of localization. In this form, stimulation of the sensory-motor areas of the cerebral cortex is followed by responses which are most prominent in the posterior portions of the vermian and paravermian lobules and in the simplex — the same areas which are activated by sensory impulses. Indeed, Adrian emphasizes the convergence upon similar cerebellar zones of impulses from the hind limb and hind-limb area of the sensorimotor cortex, and from the forelimb and forelimb area of the sensorimotor cortex, and from the face and face area of the sensorimotor cortex. The anatomical description of these cerebral projections to the vermis has been supplied by Nyby & Jansen (255). On the other hand, other frontal areas of the cerebral cortex (1, 124, 280, 360) project more strongly to the ansiform lobules over pathways which are independent of and do not require the integrity of the sensorimotor cortex (108).

Further associations between sensory projection areas of the cerebral cortex and cerebellum have been revealed by several studies directed to this specific question (149, 152, 306, 307). In the anesthetized cat, Hampson (149) and Hampson *et al.* (152) find that both auditory I and II project bilaterally to the folium and the tuber vermis only. Stimulation of Somatic I produced responses in the contralateral anterior lobe and the simplex with correspondence between hind limb, forelimb and face areas. Somatic II was reported to be related to the contralateral paramedian lobule, tuber vermis and pyramis. An area of the medial surface of the hemisphere, from which autonomic responses may be evoked, projected to the ansiform lobule, lateral anterior lobe and rostral portion of the paramedian lobule. These results have been essentially confirmed by Snider & Eldred (306) with the difference that the latter investigators recorded evoked responses from the paramedian upon stimulation of Somatic I, found equivocal results from stimulation of Somatic II and were able to detect activity only in the medial folia of Crus I and II after stimulation of the autonomic zone of the cerebral cortex. Similarly, in the locally anesthetized monkey (307) convergence of input from sensory and cerebral sources upon the same cerebellar zone has been demonstrated by stimulation of the primary sensory receiving areas of the cerebrum. As might be expected from Combs' studies (75, 76), the localization of the cerebellar response is evident only with threshold stimuli, and the degree of overlap is considerable.

Further evidence of cerebral influence on cerebellar function is furnished by the observation that stimulation of the caudate nucleus is capable of producing evoked responses in the ansiform lobule and the tuber vermis (85).

In a refreshingly different vein, it has been reported in preliminary form (166) that two different types of evoked response may be recorded from the cerebellum following single shocks to the cerebral cortex of the anesthetized cat. Short latency (2 to 5 msec.) responses may be evoked by stimulation of Somatic II while long latency (12 to 25 msec.) responses may be evoked by stimulation of Somatic I. Both of these responses are transmitted through the pontine nuclei. The individuality of these responses is further attested to by their different recovery cycles and by differences in the conditioning effect of one upon the other.

IMPULSES FROM BRAIN-STEM SOURCES. Considering the richness of cerebellar projections from various nuclear masses in the brain stem as demonstrated anatomically, there are relatively few reports of electrophysiological studies of cerebellar activation from these sources. Dow (107) has studied the cerebellar responses to single stimuli delivered to the inferior olive and to the lower bulbar reticular formation in cats. Responses were recorded from the entire cerebellar cortex as a result of olivary stimulation. The responses to reticular stimulation were different in wave form from those evoked by olivary stimulation. The latter were noteworthy for the prolonged depression following a conditioning shock. Responses evoked by stimulation of the pons were studied (107). These were found to be distributed primarily in the ansiform lobule (H VII A), the paraflocculus (H VIII B, H IX), the paramedian (H VII B, H VIII A) and the simplex and tuber vermis (VII A, VII B). Smaller and more irregular responses were recorded from the spinocerebellar projection areas.

In a study of the responses to electrical stimulation of the surface of the superior colliculus, Snider (304) recorded responses from the tuber vermis and the simplex (VI, VII A, VII B). The author suggests that cerebellar responses to visual stimulation could be mediated over tectocerebellar connections.

INTERACTIONS OF SENSORY VOLLEYS. It has already been indicated that convergence of impulses from

various sources may occur at precerebellar levels. There is also ample evidence that a high degree of convergence occurs within the cerebellar cortex itself (108, 140, 177, 179, 320). Bremer & Bonnet have devoted a series of studies to the manner of interaction between the surface negative waves which may be recorded from the unanesthetized animal in good general condition following stimulation of many afferent sources (28, 38, 39, 41). The negative wave of the test responses is completely occluded at very short test intervals, is facilitated at slightly longer intervals and undergoes subnormality at still longer intervals, whether the initiating sensory volleys come from similar sources or from sources as widely different as cutaneous and auditory. Convergence and interaction of impulses initiated by sensory and cerebral cortex stimulation have also been demonstrated by Albe-Fessard & Szabo using surface leads (3, 321) and intracellular leads (4).

Cerebellar Activity as Altered by Drug Actions

Since cerebellar neurons, seemingly to a greater extent than other neurons, are susceptible to narcotics, anesthetics and other depressing agents, the following section will emphasize the actions of excitatory agents.

TOPICAL APPLICATION. The high-voltage synchronized spikelike potential wave produced by strychnine topically applied to the cerebral cortex is a dramatic and easily reproducible event which has been studied and utilized as an investigative tool by many. The original observation of Kornmüller (175), confirmed by Dow (106) and all subsequent investigators, that strychnine applied to the surface of the cerebellar cortex does not produce hypersynchronous discharges cannot be regarded as evidence that strychnine does not stimulate cerebellar neurons. The most direct evidence of the excitant effect of strychnine has been furnished by the records of single cerebellar neurons in convulsive activity as a result of strychnine (51, 52). Cerebellar neurons, normally in tonic discharge, alter their pattern of activity under the influence of strychnine. The affected units go into an interrupted burst of discharge in which the frequency, initially within normal limits, rises progressively to abnormally high values of 400 to 500 per sec. before the termination of the burst. The diminution of spike amplitude at the higher frequency near the termination of the burst suggests that the interval between impulses becomes shorter than the refractory period. The abrupt cessation of the burst with very small spikes suggests that the burst is self-terminating by virtue of hyperdepolarization. After a variable recovery period, the sequence is repeated and continues to be repeated until the strychnine is removed. Less direct evidence of the stimulant effect of strychnine is supplied by the observation that the negative component of the evoked surface potential, related to the discharge of Purkinje cells, is augmented by strychnine (28, 42, 44). And finally, Miller's observation (207, 208) that muscular tonus and posture may be altered by local application of strychnine to the surface of the cerebellum has been confirmed many times (200, 286, 297). It has also been recorded that the discharge frequency of cerebellar neurons may be augmented by the local application of acetylcholine after pretreatment with physostigmine (90). Surface-negative responses of the cerebellar cortex, which Grundfest & Purpura ascribe to dendritic activity, are said to be eliminated by *d*-tubocurarine (141).

SYSTEMIC ADMINISTRATION. Although the local application of strychnine to the cerebellar cortex does not produce the surface potential changes characteristic of convulsive activity, the intravenous administration of strychnine to curarized animals is followed by the dramatic appearance of low-frequency (10 to 30 per sec.) high-voltage (0.1 to 0.4 mv) rhythms which have been termed cerebellar convulsions or cerebellar tetanus (42, 44, 143, 170, 171, 201–203, 289). Although it was first considered that these outbursts were truly representative of cerebellar convulsions, it has been conclusively demonstrated by Bremer and his colleagues that they are, in fact, the result of afferent volleys impinging on the cerebellar cortex from the convulsing spinal cord and brain stem (42, 44). These conclusions are derived from the following considerations. The effect of intravenous strychnine on the spinal cord is the initiation of outbursts of rhythmic convulsive activity of frequency of 10 to 30 per sec. Each tetanic wave at the cerebellar surface has a time course which is similar to that produced by an afferent volley arriving at the cerebellar cortex. The tetanic waves are localized to the bulbospinal projection areas of the anterior portion of the cerebellum. Evoked potentials and tetanic waves show mutual interaction. The phase reversal upon leading from the depths of the cerebellar cortex is similar for tetanic waves and evoked potentials. Local pentobarbital and asphyxia may abolish the negative components of both the tetanic waves and evoked potentials without affecting the positive components

which are thought to be produced by the afferent volleys. It would thus appear that systemically administered strychnine not only produces convulsive outbursts in motor elements of the brain stem and spinal cord but also initiates similar patterns of activity in ascending systems which reflexly induce the cerebellar rhythm.

Convulsive activity of the cerebellar cortex is also said to follow the administration of DDT (92) and β-chlorinated amines (261).

Cerebellofugal Activity

CEREBELLAR NUCLEI. Electrophysiological studies of the activity of the cerebellar nuclei have been carried out only recently. Arduini & Pompeiano (8, 271) have studied activity in single units of the rostral pole of the fastigial nuclei during various forms of induced activation. As would have been predicted, many of these units were tonically active. This tonic activity could be altered by surface polarization of the cerebellum (49, 50), by galvanic stimulation of the labyrinths and by stimulation of somatic sensory pathways. Cerebellar influences were most readily obtained from the vermal portion of the culmen (IV–V) and movement of the surface electrode 1 to 2 mm onto the intermediate portion (H IV, H V) was sufficient to abolish the response (see 168). Activity of units in the rostrolateral part of the nucleus was usually augmented, whereas activity of units in the rostromedial part of the nucleus was usually inhibited. Units which were not affected by cerebellar stimulation may have been related to inaccessible portions of the cortex, association neurons, or independently active fastigial elements (316).

CEREBELLAR PEDUNCLES. Electrophysiological studies of the activity patterns in the cerebellar peduncles are also rather rare. Spike discharges in the superior cerebellar peduncle of the goat have been recorded (83, 84) in response to stretch of extrinsic ocular muscles and various forms of sensory stimulation. Latencies of discharge and the finding of similar patterns in other portions of the cerebellum and cortex led to the conclusion that the activated fibers were cerebellofugal in type. Microelectrode recordings from the superior cerebellar peduncles in the decerebrate cat have revealed that a complex potential of four components may be evoked by sensory stimulation (56). Reasons are given for identifying the 25 to 30 msec. component as the efferent discharge. The evoked potential is followed by a period of electrical silence enduring for some 50 msec. In a more completely reported study, Goldman & Snider (132) describe somewhat different patterns of activity from the brachium conjunctivum of curarized cats in response to stimulation of the inferior olive, the restiform bodies and the brachium pontis. These authors ascribe a 1.0 to 1.5 msec. component of the evoked response to a monosynaptic activation of the cerebellar nuclei and a 2.5 to 3.0 msec. component to a corticonuclear relay.

ACTIVITY SECONDARILY INDUCED BY CEREBELLOFUGAL IMPULSES. Alterations in the activity of other portions of the brain induced by control of cerebellofugal activity has been studied using two different techniques. The time-honored system involving the production of synchronized volleys with single shocks and recording with microelectrodes has been used to good advantage by some (156, 310, 359). Moruzzi and his colleagues have capitalized on the responsiveness of cerebellar neurons to polarization (49, 50) and have recorded the resultant secondary changes with microwire electrodes (97, 130, 213, 293, 349, 350, 361). These studies have been concerned with secondary activity in the bulbar reticular formation, the vestibular nuclei, the midbrain and diencephalon, and the cerebral cortex.

In barbitalized cats, Snider *et al.* have recorded responses from the bulbar inhibitory reticular formation evoked by single shock stimulation of the culmen and fastigius (310). The shorter latency of the responses evoked by fastigial stimulation as compared to cortical stimulation was regarded as support for the existence of a corticofastigioreticular pathway for cerebellar inhibition. This suggestion has been strongly supported by the results of microwire reticular unit recording. Using careful anatomical and physiological controls, Mollica *et al.* (213) have been able to identify inhibitory reticulospinal units. The discharge frequency of such units was augmented by polarization of the cortex which produced collapse of decerebrate rigidity. Other units of uncertain identity were inhibited by cerebellar polarization (213, 293, 349, 350).

It has been possible to demonstrate convergence of cerebral and sensory as well as cerebellar influences on this latter type of unit (349, 350). Cerebellar inhibition was effective in decreasing the response to cerebral and sensory volleys and summed with inhibitory volleys of cerebral origin. Gauthier *et al.* (130) present evidence that the principal projection to the reticular formation originates from the vermis

proper (III, IV, V) and to a much smaller extent from the intermediate portion of the anterior lobe (H III, H IV, H V).

Convergence of cerebellar and vestibular influences on the same cells has also been demonstrated for the vestibular nuclei by DeVito *et al.* (97). The most active projection appears to originate from the spinocerebellar areas. Units of the vestibular nuclei could be stimulated or inhibited, or remained unmodified during cerebellar polarization.

Using single evoked volleys, Whiteside & Snider (359) and Henneman *et al.* (156) have examined the evoked responses of the midbrain and diencephalon (359) and cerebral cortex (156) following single shocks to the cerebellar cortex. Responses considered to be asynaptically and others considered to be transynaptically mediated were identified in many portions of the midbrain and diencephalic tegmentum and in the sensory relay nuclei of the thalamus. In experiments involving stimulation of the cortex and nuclei (156), the efferent systems were found to be extremely sensitive to barbiturates. Shocks to the anterior lobe and the simplex were followed by contralateral responses in the sensory and motor areas of the cerebrum. Paramedian stimulation evoked responses from the same areas bilaterally. It proved possible to activate the auditory area and surrounding zones by stimulation of the auditory projection zone of the cerebellum, but responses from cerebral visual areas were not recorded. Stimulation of the ansiform lobule produced irregular and inconsistent cerebral responses. From any point in the cerebellar nuclei, the cerebral sensorimotor cortices were activated bilaterally.

Perspective

Out of the details of the many studies of cerebellar anatomy and physiology utilizing electrophysiological techniques there emerge several concepts of major importance which will aid in an understanding of cerebellar function.

The first of these is the idea that even in the absence of controlled and purposeful stimuli, the neurons of the cerebellar cortex and nuclei are in a state of activity at a relatively high level. In the usual preparations studied it is impossible to refer to this as spontaneous or resting activity since there is undoubtedly a wealth of tonic afferent barrage arriving at the cerebellum from many intero- and exteroceptors and from other portions of the brain. On the other hand, it remains possible that also in the absence of the usual drive from extracerebellar sources, the cerebellar neurons may discharge in a truly spontaneous fashion. Whether this neuronal activity is truly autochthonous or whether it is driven, the level of activity is high and shows none of the tendency to synchronization which is so characteristic of the cerebral cortex. It seems reasonable to consider, therefore, that cerebellar neurons are, for the most part, very close to their critical level of excitability and that presynaptic influences exert their effects by altering the rate of discharge rather than by initiating a burst of activity from otherwise quiescent cells. In the same line of thought, the high level of activity in intrinsic cortical neurons must be reflected in a tonic discharge from the neurons of the cerebellar nuclei, and indeed this has been observed. Here again, it seems reasonable to consider that variations in cerebellar influence over extracerebellar neurons are brought about by variation of the frequency of cerebellofugal impulses, serving to produce modulation in level of excitability in the recipient neurons rather than by forcefully initiating or terminating the postsynaptic responses. That such a modulating influence may either be excitatory or inhibitory has been amply demonstrated by the studies of unitary discharges of brain-stem structures during induced variation in cerebellar activity.

The second conclusion of major importance is that cerebellar activity may be modified by cerebellopetal activity and that the potential sources for such modifying influences are extremely widespread. It is no longer adequate to consider cerebellar functions in relation to the proprioceptive system alone. While it is undoubtedly true that impulses from proprioceptive receptors constitute one of the major sources of cerebellar input, it is equally true that other varieties of sensory input and input from other portions of the brain cannot be neglected in any attempt to understand cerebellar function. Many of the sources of cerebellopetal impulses have been defined anatomically for years, and the electroanatomical studies in such cases have served largely to confirm and to refine the findings of the older investigations. The new information derived from electroanatomical investigations emphasizes the effectiveness and the distribution of impulses from auditory, visual, cutaneous and interoceptive sources as additions to the proprioceptive input. It is important to understand also that, even though the surface sign of the evoked potential is essentially the same for all cerebellopetal pathways, the physiological effects of the cerebello-

petal influence may consist of inhibition as well as of excitation.

The complete significance of the variety of sources of cerebellopetal influences will become clearer as the information concerning the results of stimulation and extirpation is developed later in this chapter. At this juncture it is sufficient to point out that in order to bring about coordination of reflex and voluntary movements, the cerebellar mechanisms require a continuous flow of information from all possible sources. Complex motor acts such as that of deglutition, or of shifting visual attention from one to another object of regard, could scarcely be properly coordinated without the assistance of sensory impulses of interoceptive origin or of visual origin nor without the information carried by impulses originating from the volitional mechanisms of the cerebral cortex.

The demonstration of the existence of localized receiving zones for some forms of cerebellar input, and the contrasting demonstrations of more or less diffuse and overlapping receiving zones for cerebellopetal impulses, have left unsolved many old problems of localization of function in the cerebellar cortex. The overlap of spinocerebellar and cerebrocerebellar projections in the anterior lobe was predicted on the basis of histological studies and completely nullifies the concept that the paleocerebellum is the exclusive mediator of spinocerebellar relationships. On the other hand, if it is granted that the paramedian lobules may be activated by association fibers (169), what has been called the neocerebellum may indeed be regarded as the exclusive mediator of cerebrocerebellar relationships. Within that portion of the cerebral cortex which is shared by spinocerebellar and cerebrocerebellar input, and which is also related through the fastigius and interpositus to extracerebellar structures, the significance of the localized areas for afferent projection remains uncertain. As Combs himself points out, there are serious anatomical objections to calling upon the lateral reticular nucleus of the medulla to bear the entire burden of such localized projections as have been demonstrated. When experimental conditions are proper for the observation of unlocalized activity within this portion of the cerebellum, it is impossible to say at present whether this is the result of a truly diffuse projection, in the physiological sense, or whether the projection is actually to specific cortical neurons which are not segregated into special compartments on a somatotopic basis.

The third concept of importance which derives from the electrophysiological studies consists in the striking and dramatic evidence afforded by microwire studies of unit discharges from brain-stem nuclei of the manner in which cerebellar mechanisms operate with respect to the primary transmission pathways of the brain. In the light of these findings, it seems not unreasonable to regard the cerebellofugal impulses as playing their role by modulating the excitability of key neurons in transmission pathways which receive their principal activation from sensory sources or sources higher in the brain. By converging upon neurons primarily activated from other sources, cerebellar impulses might be able to exert an important control over traffic on the pathway even though the pathway does not, anatomically, course through any part of the cerebellum.

FUNCTIONAL ALTERATIONS PRODUCED BY CEREBELLAR STIMULATION

The major portion of the work reported during the nineteenth century must be regarded as almost useless because of the failure of investigators to differentiate carefully between responses produced by cerebellar stimulation and those produced by stimulation through spread of current to nearby brainstem structures. It must be remembered that the characteristics of excitability of neuronal structures were very poorly understood and that techniques for the control of stimulating pulse parameters were practically nonexistent. For more complete information concerning these earlier papers the reader should consult van Rijnberk (346–348), Brun (53), Spiegel (315) or ten Cate (324).

In 1897 Lowenthal & Horsley (187) and Sherrington (295) first described inhibitory reactions which were certainly due to stimulation of the cerebellar cortex. Nevertheless, Horsley & Clarke (160), describing experiments on anesthetized animals, later concluded that the cerebellar cortex was not excitable by direct electrical stimulation. This erroneous conclusion coupled with the fact that many investigators were looking for phasic movements such as those produced by stimulation of the cerebral cortex, served to impede progress in this line of experimentation for many years. Since that time, the realization that anesthesia severely depresses responses to cerebellar stimulation has conditioned the choice of experimental preparation with the result that a great many investigations have been carried out on unanesthetized decerebrate animals. This

means that the larger share of observations have dealt with responses which are superimposed upon the abnormal background of decerebrate rigidity. This fact has certainly colored the general viewpoint of cerebellar function as revealed by stimulation in such a fashion as to emphasize the role of the cerebellum in relation to postural reactions.

Due to technical difficulties, cramped spatial relations and a certain lack of interest, the literature on the reactions of submammalian forms to cerebellar stimulation is quite scanty. The major portion of such investigations has been carried out on birds, and the results serve to establish the general similarities of avian responses to mammalian responses, although some very interesting specific questions have been raised (34, 43, 46, 70, 192, 193, 200).

Stimulation of Cerebellar Cortex

ELECTRICAL STIMULATION. Any attempt at a brief exposition of the studies of responses to electrical stimulation of the cerebellum is complicated by several difficulties. Since the cerebellum is so sensitive to general depressing influences, it is no surprise to encounter variations in results from one study to another. The significance of anatomical details has not been appreciated by all investigators with the result that foci of stimulation are not always clearly described. The responses themselves are complex and often appear in opposite sign in various limbs. In the following, the attempt is made to divide the material anatomically and to discuss further on the basis of a functional subdivision in terms of response types.

Anterior Lobe: Vermian Portion. Cerebellar cortical stimulation in the vermian portion (between the paravermian veins) may give rise to a decrease, inhibition, or an increase, facilitation, of pre-existing motor neuron discharge. Since the inhibitory responses have priority both by virtue of longevity and by sheer weight of paper devoted to their descriptions, they will be considered first.

As indicated earlier, Sherrington (295) and Lowenthal & Horsley (187) first described inhibition of decerebrate rigidity during cerebellar stimulation in cats, dogs (187) and monkeys (295). The collapse of rigidity was said to be prompt and complete on the ipsilateral side but also involved contralateral limbs. There followed a long period during which anterior lobe stimulation was not effectively used as an investigative tool, a silence that was broken by Bremer's classic papers describing the inhibitory response in greater detail and describing also the powerful rebound contraction at the end of stimulation (32).

Since that time, the inhibition of tonus accompanying cerebellar stimulation has been the subject of numerous studies (23, 33, 35, 96, 210, 221, 232–238, 309, 310, 317). Many of these studies have made contributions to the presently held conclusion that inhibition of decerebrate rigidity on the ipsilateral side is the result of stimulation of the truly vermian portion of the anterior lobe with threshold shocks above 40 per sec. It has been demonstrated (152) and confirmed (236, 310) that there is a certain degree of somatotopic localization within the area under consideration in that the forelimb is most easily affected from the culmen (IV, V), the hind limb from the centralis (III) and the tail from the lingula (I). This somatotopic arrangement is easily obliterated by slightly suprathreshold stimulation (267, 268). The inhibition of forelimb extensor tonus is not reciprocal inhibition of spinal origin since it is not accompanied by contraction of the flexor muscles and since it develops more slowly, lasts longer and shows recruitment (32, 96, 237, 317). The extensor inhibition is extremely powerful in the sense that it cannot be overcome by maximal vestibular and proprioceptive reinforcement of decerebrate tonus (222–224).

It is also important to note that inhibition of many other activities of the brain and spinal cord may also be observed during stimulation of the vermian portion of the anterior lobe. Not only is decerebrate tonus decreased by cerebellar stimulation, but the crossed extensor reflex and its myotatic appendage may also be obliterated (32, 219). The running movements of high decerebrates may be halted (32) and the somatic and autonomic components of sham rage in the thalamic animal may be held in abeyance (231). Vasomotor reflexes (225, 226) and galvanic skin reflexes (355) are among some of the simpler autonomic functions inhibited by cerebellar stimulation. Movements induced by chemical (227–229) and electrical (309, 310) stimulation of the cerebral cortex may be blocked by cerebellar inhibition. The strychnine convulsion of the spinal cord (37) may be reduced in frequency but not in amplitude by cerebellar inhibition (330, 331). And finally, of utmost importance, is the observation that gamma neuronal activation of muscle spindles may be inhibited by cerebellar stimulation (134, 137).

In spite of these numerous observations of the powerful and widespread inhibitory effects of stimulation of the anterior lobe vermis, the same cerebellar

areas may also give rise to facilitatory influences. These have appeared in three basic forms: *a*) augmentation of extensor tonus in the ipsilateral forelimb, *b*) augmentation of extensor tonus in the contralateral forelimb, and *c*) augmentation of ipsilateral extensor tonus as a postinhibitory rebound phenomenon.

Augmentation of ipsilateral extensor tonus and of extensor reflex contractions was noted from time to time as an unexplained deviation from the usual experimental findings (32, 96, 220). The suggestion (96) that the anterior lobe contains a mixture of cells of opposite potentialities received strong support from observations by Moruzzi (232–238) that extensor inhibition was converted into extensor facilitation by the simple maneuver of lowering the frequency of stimulation. This observation has been confirmed (47, 331–334) and indicates that the anterior lobe vermis has the double potentiality for inhibition and facilitation over frequency selective efferent paths. The preponderance of inhibitory observations is probably due to the prevalence of the use of stimuli in excess of 30 to 40 per sec. which activate the powerful and overwhelming inhibitory mechanisms.

The augmentation of contralateral extensor tonus in the decerebrate animal which has been emphasized so strongly by Sprague & Chambers (317) as a predictable result of stimulation of the anterior lobe vermis may now be regarded as an established and regular event accompanying stimulation with slightly higher voltages than required for ipsilateral inhibition. These observations have been confirmed (267, 268) with the added information that contralateral augmentation of extensor tonus is supplanted by contralateral inhibition such as originally seen by Sherrington (295) and by Lowenthal & Horsley (187) if the voltage of stimulation is increased slightly more. If activation of the contralateral side of the cerebellum, or of its efferent pathways, is surgically prevented, the contralateral inhibition of tonus with higher voltages disappears and the augmentation reappears.

The remarkable and dramatic augmentation of ipsilateral extensor tonus following inhibitory stimulation, post-inhibitory rebound (32), is the third form of facilitatory reaction which may be evoked by cerebellar stimulation. Despite its clear and regular manifestations, it still remains unanalyzed. It is possible that rebound contractions are not, strictly speaking, to be ascribed to cerebellar discharge continuing after the cessation of the stimulation.

Anterior Lobe: Intermediate Portion. The first reliable evidence that the anterior lobe is not equipotential over its entire surface was derived from the studies of Stella (318) who noted facilitation of ipsilateral forelimb tonus which was not abolished by removal of the vermal portion of the anterior lobe. These results were soon confirmed and extended by Hampson *et al.* (150–152). In quadrupeds only the medial three fifths or vermal portion of the anterior lobe gave rise to the type of responses just described in the preceding paragraphs. The stimulation of the lateral two fifths, or intermediate portion, on the other hand, produced ipsilateral extensor facilitation coupled with flexor rebound. These observations were confirmed in the quadruped (230) and in the monkey (151). The monkey shows a broader extension of the facilitatory response, a species difference which was also noted by Snider *et al.* (310). Sprague & Chambers (317) also point out that increasing the strength of stimulation augmented the intensity of the response but did not alter its quality. Working with decerebrate preparations which had been subjected to chronic destruction of the fastigial nuclei to eliminate all responses from the vermis, and by careful attention to the state of the preparation and to selection of stimulus parameters, Pompeiano (269, 270) has been able to evoke two types of responses regularly from the intermediate portion of the anterior lobe. He divides it into a medially placed strip from which may be elicited ipsilateral active flexion and contralateral extension (23, 96, 150, 152) and a laterally placed strip the stimulation of which brings about ipsilateral extensor facilitation (150, 230, 317, 318). It was presumably during activation of the lateral strip that Granit & Kaada (137) made the very significant observation of augmented gamma neuron discharge (see also 134).

Anterior Lobe: Efferent Paths. The distribution of the efferent pathways mediating these various responses has been clarified by physiological experiments guided by the detailed anatomical studies of the Oslo school (169).

Sprague & Chambers (317) have reported that responses characteristic of the vermal portion of the anterior lobe are duplicated by stimulation of the nuclei fastigius, the inferior cerebellar peduncle and the medial reticular formation of the medulla, observations which have been confirmed by Ricci & Zanchetti (279). These results thus support the observations of Bernis & Spiegel (23) that inhibition from the anterior lobe vermis is abolished by section of the inferior cerebellar peduncle.

In a careful series of experiments, Moruzzi &

Pompeiano (243, 245, 246) have demonstrated a functional subdivision in the fastigial nucleus. Small, highly selective lesions in this nucleus have enabled them to differentiate the pathways for vermal ipsilateral inhibition and vermal ipsilateral facilitation. Inhibitory activity courses through the rostrolateral portion of the nucleus and facilitatory activity is mediated by the rostromedial portion of the nucleus. Both paths then rejoin in the ipsilateral inferior cerebellar peduncle.

Pompeiano (267, 268) has demonstrated that the contralateral augmentation of extensor tonus accompanying slightly suprathreshold stimulation of the anterior lobe vermis is dependent upon fastigiobulbar fibers which cross after leaving the cerebellum. Evidence is also offered suggesting that the total response is organized by bulbar or spinal mechanisms.

The ipsilateral facilitatory response to stimulation of the hemispheral portion of the anterior lobe may be duplicated by stimulation of the nuclei interpositus, superior cerebellar peduncle and lateral reticular formation of the medulla (317). In cats with chronic fastigial lesions, it has been found that responses of the two hemispheral strips (245, 270) are mediated through the anterior one third of the nucleus interpositus. It would appear that the ipsilateral flexor response from the medial strip courses through the medial side of the cephalic portion of the nucleus while the ipsilateral facilitation of extensor tonus from the lateral strip courses through the lateral side of the cephalic portion of the nucleus.

The course of these pathways within the brain stem has been the subject of some investigation. Inhibitory responses to vermal stimulation are still obtainable after postcollicular decerebration (219, 234, 310) and so must be mediated through pathways confined to the lower pons and medulla. However, it has been demonstrated (23, 32) that rigidity increases after postcollicular decerebration as though some inhibitory influences were operating over the superior peduncle and mesencephalic pathways. Hare, Magoun & Ranson (153) suggested that such activity might be conveyed over fibers of the brachium conjunctivum descending from the level of the red nucleus. Pompeiano's (270) observations indicate that the ipsilateral flexor response from the medial strip of the hemispheral portion of the anterior lobe is conveyed over a doubly crossed pathway involving the contralateral red nucleus. Thus, this response would not be obtainable in postcollicular preparation. The ipsilateral extensor facilitation, on the other hand, persists after postcollicular decerebration and is organized at the medullary level.

The results of Nulsen *et al.* (254a) which have appeared only in preliminary form have not been confirmed physiologically and cannot be reconciled with present anatomical information.

The spinal pathways of these cerebellar responses have not been clearly isolated as discete tracts. It would appear that (163, 269) the descending impulses are conveyed over diffusely scattered fibers in the lateral and ventral funiculi which do not cross at the spinal level. This description of transmission pathways is the same as the description of the reticulospinal tracts (254).

Anterior Lobe: Locus of Action. The locus of these facilitatory and inhibitory effects has not been clearly determined. The suggestion has frequently been made that the inhibitory action is located in the spinal cord (96, 219, 330, 331). However, in view of the influence of cerebellar discharge upon the reticular formation (310, 349, 350) and on the vestibular nuclei (97), it is possible that the inhibitory effects may appear as the result of cessation of facilitation from inhibited brain-stem structures. Although no data have been presented, it is also possible that the facilitatory effects may be equally indirect. Granit *et al.* (135) stress the necessity for considering both the alpha and gamma motor neurons as final common paths for cerebellar influences.

Posterior Lobe: Postural Tonus. The occurrence of responses similar to those obtained from the anterior lobe has also been reported as a result of posterior lobe stimulation. Among the reactive foci are the simplex (VI, H VI) (152, 334), pyramis (VIII A, VIII B) (32, 152, 317, 334), uvula (IX) (317) and paramedian (H VII B, H VIII A) (152, 308, 310, 317). One gains the impression that these responses are not as reliably produced or as powerful as those derived from stimulation of the anterior lobe.

Posterior Lobe: Eye Movements. Conjugate deviation of the eyes has been reported as a result of posterior vermis stimulation by numerous investigators (36, 86, 104, 112, 152, 153, 161, 231, 233, 250). These have been obtained from the folium and the tuber vermis (VII A, VII B), simplex (VI) and pyramis (VIII A, VIII B).

Posterior Lobe: Cerebral Cortex. It is notable that movements or alterations of tonus as primary events resulting from cerebellar stimulation have almost exclusively been related to the stimulation of vermal structures in the anterior and posterior lobes. Nevertheless, stimulation of the cerebellar hemispheres,

while not productive of primary alterations of motor neuron activity, has been found capable of altering the motor functions of the cerebral cortex. This influence of the cerebellar cortex upon phenomena related to cerebral function has been demonstrated in terms of *a*) changed cortical excitability to chemical and electrical stimulation, *b*) alterations produced in movement evoked by stimulation of the cerebral cortex and *c*) alterations in the electrical activity of the cerebral cortex. In order to avoid presenting the distorted impression that only hemispheral stimulation alters cerebral function, it will be more convenient to consider these studies in a separate section devoted to cerebellocerebral relations.

Flocculonodular Lobe. The flocculus and nodulus (X, H X) are so near the medulla that effective stimulation localized to this portion of the cerebellum probably has never been achieved (251, 287).

OTHER FORMS OF STIMULATION: *Chemical.* Of the older studies of chemical stimulation, perhaps the most demanding of attention were those of Pagano (257, 258). Pagano reported experiments performed on unanesthetized dogs wherein he stimulated the cerebellum by injections of curare into the substance of the cerebellar cortex. Injections into the hemisphere were reported to produce ipsilateral tonic movements followed by generalized seizures, the later dependent upon the motor cortex. Similar injections into the vermis were reported to produce behavior patterns like those seen in deep anxiety and extreme fear. Pagano's conclusions concerning the role of the cerebellum in the sphere of emotion and emotional expression aroused considerable controversy which has been reviewed by ten Cate (324) and van Rijnberk (348).

In later years, chemical stimulation, principally with strychnine, has been used largely as a control procedure to verify the cortical origin of responses to electrical stimulation of the cerebellar cortex (207–209, 298). The reported observations fall well into line with observation of responses to electrical activation.

Mechanical. Mechanical stimulation presumably produces its results by initiating a discharge of impulses from injured and dying cells and thus is not a reversible procedure. It does have the advantage that local injury of the cerebellar cortex will produce responses which can reliably be interpreted as originating from the injured focus, rather than from some nearby structure. Clark's studies (71) with their excellent histological controls are undoubtedly the most reliable of this group. Mechanical stimulation produces the same pronounced responses and prolonged aftereffects as electrical stimulation in the unanesthetized animal. The results of electrical stimulation will be described in detail below.

Stimulation of Interior of Cerebellum

The original studies of Horsley & Clarke, in which the first application of the stereotaxic technique was made (160) were carried out on deeply anesthetized monkeys, and while responses were produced by stimulation of deeper portions of the cerebellum the profundity of anesthesia undoubtedly interfered with the reliable demonstration of function. Poorly controlled studies were also made by others (250, 291).

Miller & Laughton (211, 212) stimulated the surgically exposed cerebellar nuclei in decerebrate cats and, in spite of trauma and poor general state of the preparation, were able to obtain reliable responses. Activation of the dentate nucleus was accompanied by ipsilateral foreleg flexion with little contralateral effect. The interpositus and the globosus produced similar forelimb flexion accompanied by contralateral extensor inhibition, the cessation of stimulation being followed by rebound. Activation of the fastigius produced strong active flexion of both forelimbs with powerful rebound.

The technique of Horsley & Clarke has been reapplied to lightly anesthetized cats (154, 196), decerebrate cats (153) and lightly anesthetized monkeys (195). Several varieties of responses were obtained during careful mapping of the interior of the cerebellum which cannot be completely reviewed here. It is enough to note that dentate stimulation was not characterized by any specific variety of responses. Stimulation of the intermediate nuclei produced local limb responses consisting of relaxation from any existing posture followed by poststimulation rebound to that posture. Fastigial stimulation produced responses in all four limbs, flexion ipsilaterally and extension contralaterally, with strong poststimulation rebound which was not dependent upon afferent activity from limb proprioceptors or vestibular afferents.

The serial stimulation of portions of the cerebellum in an attempt to define the cerebellofugal pathways has been mentioned in the section devoted to that subject. In addition to such studies, others have been devoted primarily to a definition of the responses to nuclear stimulation in selected portions of the cerebellar nuclei in decerebrate cats. Stimuli applied to the caudal pole of the fastigius reproduce the results

of stimulation of the pyramis in that they induce ipsilateral inhibition and contralateral facilitation of rigidity (244, 247). Stimulation of the interpositus is reported to produce an increase in ipsilateral rigidity (272), but the flexor rebound noted by previous investigators (153, 154, 317) was not observed. Koella notes that influences upon decerebrate rigidity originating in the labyrinths summate with the effects of stimulation of various points in the interior of the cerebellum (173). The same author has also described the complicated movement patterns which may be provoked in the unrestrained unanesthetized animal by stimulation of the medial basal portions of the cerebellum (174).

Cerebellocerebral Interactions

It was indicated earlier that influences originating in the cerebellar cortex have been shown to affect the motor functions initiated at the cerebral cortex and the electrical activity of the cerebral cortex.

MOTOR FUNCTIONS. Cerebellar stimulation has been demonstrated to influence motor functions of the cerebral cortex using both the threshold to stimulation and the responses evoked by stimulation as criteria for study. Rossi's original observation (282) that the threshold of the motor cortex to electrical excitation is lowered during stimulation of the ansiform lobules (H VII A), paramedianus (H VII B, H VIII A) and the posterior vermis (VI to IX) have been adequately confirmed (36, 114). No somatotopic arrangement was detected in these studies.

Lowenthal & Horsley (187) early reported that movement evoked by stimulation of the motor cortex was augmented by stimulation in the area of the lateral vermis near the hemisphere. Using both the convulsive discharge of the motor cortex occurring during chloralose anesthesia as well as strychnine-induced clonus, Moruzzi (227–229) has described both facilitatory and inhibitory results from stimulation of the cerebellum. With stimulation of the culmen (IV, V) phasic and clonic movements would break through a background of tonic inhibition. From the ansiform lobule (H VII A) subthreshold convulsive activity could be converted into overt convulsions. As was the case for decerebrate rigidity and for reflexly evoked contractions, cortically-induced phasic movements were also inhibited (309, 310) by stimulation of the culmen (IV, V) in the cat and more predominantly augmented by anterior lobe stimulation in the monkey (308). From the intermediate and lateral parts of the vermis and from the paramedian lobules, evidence of somatotopic organization was derived (308).

The question of locus of these effects has not been dealt with critically. Facilitation and increase of excitability may be a cortical or a brain-stem function, as may be inhibition (6, 349, 350).

ELECTRICAL ACTIVITY OF CEREBRAL CORTEX. Two types of alteration of electrocortical activity have been described as resulting from cerebellar stimulation. Walker observed an increase in the rate and amplitude of cortical waves in the motor areas of the cat 'encéphale isolé' during stimulation of the cerebellar hemispheres (353). Similar effects have been observed as a result of application of strychnine to the lobulus ansiformis (H VII A) and appear only in the contralateral sigmoid gyrus (60). Picrotoxin, prostigmine, pentylenetetrazol (Metrazol) and diisopropylfluorophosphate (DFP) produce similar changes when applied to the ansiform lobule (88). On the other hand, electrical (87, 213, 242) and chemical (88) stimulation of the vermis converts the rhythmic activity of the resting cortex into the low voltage fast activity of the arousal and initiates changes in the steady potential of the cortex (103). Even seizure activity is reported to be desynchronized by cerebellar stimulation (305). Cooke & Snider (80) indicate that this sort of change can be produced from many portions of the cerebellum and interpret their results as indicative of a localized cerebellocerebral relationship.

It appears most probable that the localized effects on the motor cortex are mediated over the dentatorubrothalamic pathways whereas the production of a generalized activation pattern is a function of cerebelloreticular paths.

Stimulation Through Chronically-Implanted Electrodes

Recognizing the barriers to the acquisition of complete information presented by the necessity for working either in the presence of depressing anesthesia or, alternatively, against the background of disturbed postural tonus of the decerebrate animal, several studies have been carried out using chronically-implanted electrodes to stimulate the cerebellum in freely-moving unanesthetized animals.

From points scattered over the ansiform lobules (H VII A), the paramedian (H VII B, H VIII A) and the posterior vermis (VI–IX), and from a few points on the posterior edge of the anterior lobe (V),

Clark (72) reports that complicated patterns of movement may be evoked by electrical stimulation. These patterns are constant from day to day and differ from point to point. The response pattern starts with the production of a sustained abnormal posture during the stimulation, forceful rebound immediately after the stimulation and then continues in a long sequence of bizarre postures lasting several minutes as they progress in slow lesiurely fashion from one part of the body to another. Similar 'seizures' are produced by mechanical stimulation (71) and by stimulation of certain interior portions of the cerebellum (65). The 'seizure' is present after bilateral cerebral decortication and deafferentation (73, 74).

If the cerebellum is split in the mid-line, the 'seizure' is unilateral but is capable of crossing small bridges of intact cortex anteriorly and posteriorly. McDonald (205) has repeated this type of experiment using implants on the anterior lobe. During stimulation, slow collapse of extensor tonus occurs in the ipsilateral forelimb or hind limb, depending upon the location of the electrode. This is at times accompanied by contralateral extension and is followed by post-stimulation rebound and seizures. Sprague & Chambers (317) indicate that with threshold stimuli applied to the fastigial nucleus, the same responses are seen in the unanesthetized as in the decerebrate animal, and that if the voltage is raised seizures may occur.

Perspective

The organization of this portion of the chapter on the cerebellum was constructed in an attempt to help the reader discover the meaning and significance of the varieties of experiments which have dealt with cerebellar stimulation. Certainly this is a difficult task in the light of the amount of data which has been accumulated. Even more difficult is the task of understanding the details of the mechanisms involved in the production of responses to cerebellar stimulation. It is obvious, particularly in this last respect, that we do not yet know enough to arrive at any clarity of understanding. However, certain superficial generalities may be worth emphasizing in the way of a summary, even if the remarks only repeat what has been said many times before.

In spite of the bias introduced through the use of the decerebrate preparation in so much of this work, it nevertheless remains clear that cerebellar activities are principally related to the adjustment of tonus of striated muscle. This is simply a different way of saying that the initiation or precipitation of motor neuron discharge does not seem to be the principal task of the cerebellum. Instead, its forte is in the adjustment and regulation of the time-space pattern of motor neuron discharge precipitated by activity in some other portion of the nervous system. This appears evident from the time course of the reactions to cerebellar stimulation which are somewhat more leisurely and prolonged than those resulting from cerebral or reflex stimulation. It also may be inferred from the manner in which cerebellar influences add to and subtract from the potency with which cerebral and reflex mechanisms may govern motor neuron activity.

While the function of the cerebellum as a whole may be regarded in this general light, there are indications that not all portions of the cerebellum are equipotential insofar as the mechanisms through which these influences are brought about are concerned. Since so little has been accomplished with the vestibular portions of the cerebellum in experiments involving stimulation, it is justifiable to dismiss this portion from our present considerations. The most important differences relate to the mechanism of function of the anterior and posterior lobes. The differences are not mutually exclusive and sharply defined, but in the present state of our knowledge it seems justifiable to emphasize them.

The anterior lobe would appear to be concerned primarily with the regulation of motor neuron response to reflex control mechanisms. In the execution of this function its influences are exerted upon descending pathways involving portions of the extrapyramidal motor nuclei such as the red nucleus, the reticulospinal systems descending from the brainstem tegmentum and the vestibulospinal systems. There is ample evidence that both facilitatory and inhibitory capabilities, necessary to proper operation of any control system whether biological or physical, are also possessed by this control system. While the pathways over which these functions leave the cerebellum have been fairly well clarified, it remains uncertain whether the final mechanism is uniform for all aspects of function. For example, we still do not know whether all inhibitory responses are brought about by cerebellar activation of a brain-stem inhibitory mechanism or whether some may be brought about by cerebellar inhibition of a brain-stem facilitatory mechanism. The fact that the cerebellum also participates importantly in the control of the gamma motor neurons as well as in the control of alpha motor neurons is a new and promising observation which

dictates the reanalysis of many aspects of responses to cerebellar stimulation.

The posterior lobe, particularly the hemispheral portion, in keeping with its phylogenetic history, seems to turn its attention in the other direction, toward the modification of cerebral control of motor neuron discharge. This is in part inferred from the paucity of reports of movement initiated by stimulation of the hemispheres. It is likewise inferred from the fact that the thresholds to stimulation of the motor and electrical activity of the motor cortex are altered during hemispheral stimulation. The evidence is not yet clear as to how much of this 'upstream' influence from the cerebellum influences the cerebral cortical functions themselves. Certainly the alterations in electrical activity and probably the alterations of excitability represent a response of the cerebral cortex per se. On the other hand, the various alterations produced by cerebellar stimulation during movement evoked by stimulation of the cerebral cortex may, and probably do, depend upon alterations in excitability produced somewhere along the subcortical pathway to the motor neuron, and perhaps even at the motor neuron.

Although segregations and sequestrations of function such as those just outlined are attractive in that they seem to help create order in a confused situation, they cannot be adhered to dogmatically. Surely, there are evidences of overlap and the margins are not clear. And this is as it should be, for in any well-run organization it is essential for the 'right hand' to know what the 'left hand' is doing. Thus, alterations of cortically-induced function may be obtained from the anterior lobe and alterations of tonic motor neuron activity may be obtained from the posterior lobe. The potentialities for communication within the cerebellum are tremendous on the basis of solely anatomical considerations. That there is functional order within this rich network is strikingly demonstrated by the stability of the patterns of induced cerebellar seizures in unanesthetized animals.

From the anatomical point of view, somatotopic organization within the efferent pathways from the cerebellar cortex is of a high order as regards cortico-nuclear relations (169). However, beyond this point, anatomical data are inadequate to support the functional evidences of somatotopy which have been noted. It is important to recognize that such functional evidence of somatotopic relations is demonstrable only with threshold stimuli and disappears under conditions conducive to intracortical spread of activity.

ALTERATIONS OF FUNCTION PRODUCED BY CEREBELLAR DESTRUCTION

Introduction

Nothing could be more logical than to attempt to define the function of an organ by noting the deficiencies suffered by an organism after its destruction in whole or part. Although this method of approach to cerebellar physiology has the longest and the most crowded history, many of the studies have not been susceptible of accurate interpretation. Here again, the drawbacks introduced through lack of anatomical knowledge and lack of attention to histological controls have resulted in a great deal of confusion, particularly in the older literature. Lesions made surgically were not always confined to the areas intended; secondary destruction resulting from disturbances of blood supply occurred; and lesions resulting from simple exposure and from inadequate closure techniques complicated the picture (122). Further difficulties arose through lack of understanding of terms used to describe deficiencies, and some of the most hotly contested points seem to have hinged on definitions and methods of examination designed to display deficiencies. On the other hand, these defects are by no means universal, and much of the older work has been repeatedly confirmed by later investigators. The studies of the results of ablation of cerebellar material bear out the overwhelming importance of the cerebellum in relation to the control of motor neurons which was revealed by the studies of responses to stimulation. Before entering into a consideration of the ablation experiments, it would be well to consider the meanings of some necessary words and phrases without which the description of cerebellar signs would be chaotic.

We owe to Sherrington (296) the clean definitions of the two basic types of function subserved by striated muscle. Striated muscle may serve in the 'maintenance of attitude' through the development of a continuous isometric contraction. This type of contraction he called postural tonus. Sherrington emphasized the importance of postural tonus in antagonizing gravity but also called attention to the role of postural tonus in the maintenance of various portions of the body in stable relationship to each other. Striated muscles may also serve as 'organs of motion,' engaging in brief periods of activity serving to move the whole body or its parts. Such contractions are phasic in their nature and may originate through reflex or voluntary activation. This distinction between postural tonus,

reflexly-evoked phasic contractions and voluntarily-controlled phasic contractions is an important one which should be borne in mind.

Through the many years of endeavor on the part of physiologists and clinicians to describe the disorders of posture and movement following cerebellar lesions, a complicated terminology developed in which similar words were often used with different meanings. We owe to Holmes (158) the present system of definitions which he evolved in his classic papers on cerebellar disease in man. This nomenclature was soon adopted by clinicians. Walker & Botterell (354) introduced these definitions into the physiological literature and they have been generally used by physiologists since that time. The most important of these terms are: *a*) cerebellar ataxia, a general term embracing all motor phenomena of cerebellar deficiency including dysmetria, tremor, decomposition of movements, etc.; *b*) dysmetria, any disturbance in the range of voluntary movement; *c*) hypermetria, an excessive range of movement or overshooting; *d*) hypometria, deficient range of movement resulting in a failure to reach a goal; *e*) decomposition of movement, deficiency in the proper sequence and timing of the components of a motor act; *f*) tremor, trembling or oscillatory movements at rest (static tremor), during an active movement (kinetic tremor) or the coarse 'hunting' oscillations occurring at the time of approach to a goal (terminal tremor); *g*) tonus, the slight constant tension of healthy muscles which contributes a slight resistance to passive displacement of a limb; and *h*) hypotonia, deficiency in tonus manifest as a diminished resistance to passive movement.

All submammalian forms have been subjected to a certain amount of experimentation with varying degrees of control and with varying degrees of productiveness. The older literature on these forms has been reviewed by ten Cate (325 to 327). Bremer and his colleagues (34, 45) and Chiarugi & Pompeiano (69) have more recently done carefully controlled studies on the ablation of the cerebellar cortex and nuclei in birds. Space limitations permit only the observation that these studies demonstrate that, in some respects, birds react differently to cerebellar ablation than mammals and that special problems are thus encountered. Nevertheless, the decerebellate bird has been reported to show an exaggerated positive supporting reaction (45) comparable to that later described in the mammal (277).

Total Ablation

The many experiments performed by Luciani, extending over a span of 10 years, first described in Italian in 1891 (188), later in German (189) and then in English (190), still stand as a solid foundation underlying the results of later studies on the effects of cerebellar ablation. Although his descriptions have not gone without challenge from time to time, there is at present almost no need for change or emendation. Luciani divided the postoperative course of his animals into three phases. His first stage constituted a period of excessive motor activity, a period of dynamic signs which he referred to as 'functional exhaltation.' The second stage was a period during which motor deficiencies were the outstanding characteristic of the animal's behavior. The third stage constituted a stable state which developed as the animal became able to compensate for his deficiencies. Luciani gave reason to consider that compensation occurred in two ways: *a*) through a process of organic compensation involving new activities on the part of remaining portions of the brain and *b*) through a process of functional compensation by virtue of which the animal learned to correct the deficits produced by cerebellar ablation. As Moruzzi & Dow (241) point out, the processes of compensation undoubtedly start immediately after the production of a cerebellar lesion. For this reason they consider it more logical to subdivide the postoperative course into a period of unstabilized deficiencies and a period of stabilized deficiencies. In the paragraphs to follow, an attempt will be made to describe the various manifestations of cerebellar removal in terms of their functional nature, considering first the subprimate forms and indicating the important differences which have been noted in the primates.

SIGNS OF INHIBITORY WITHDRAWAL. During the first 5 to 10 days following total removal of the cerebellum, dogs and cats are agitated and restless. They are unable to stand, and, lying in the cage, exhibit periods of exaggerated opisthotonus coupled with rigid extension of the forelimbs, alternating clonic movements of the hind limbs and ocular convergence (113, 114, 182, 183, 188–190, 274–277, 335). As improvement occurs and the animal attempts to attain the upright posture, the forceful extension of the forelimbs often throws the animal over onto its back.

Luciani was unable to establish firmly the reason for this behavior, considering it most probably to be due to irritation and injury discharges from the site

of the ablation. The establishment of the role of inhibitory withdrawal in the production of these signs grew out of the observation that decerebrate rigidity is remarkably augmented by removal of the cerebellum (22, 32). It remained only for Pollock & Davis (262–265) through the reduction of cerebellar function by ischemia, and Camis (58, 59) through the use of cold, to demonstrate that injury discharges were not essential for the production of the signs of overactivity. These latter investigators went a step further with their demonstration of the importance of the vestibular system in the production of these signs through its excessive facilitatory influences on spinal cord motor functions. Although at this stage of the animal's recovery the major signs involve what might be regarded as postural mechanisms, it was early noticed that some reflex activities also share in the effects of inhibitory withdrawal. Tendon reflexes (182, 183, 335) and many reflexes involved in the maintenance of stance (277) become hyperactive and remain so for months following the ablation.

The immediate postoperative signs of inhibitory withdrawal are remarkably mild in the monkey as compared to the quadruped (9, 123, 188–190, 249, 290). This form shows no opisthotonus, the forelimbs are not rigidly extended but held in the flexed posture, and the signs of functional exhaltation disappear in 2 to 3 days.

SIGNS OF FACILITATORY WITHDRAWAL. As the quadruped begins to compensate for the overpowering release from tonic inhibition, it begins to demonstrate evidence of reduced motor neuron discharge giving rise to signs which Luciani (188–190) called atonia and asthenia. With the first attempts to right itself and to assume the standing posture, the animal's hind legs are completely devoid of weight-bearing function. Even the forelegs fail to sustain weight for long. Later, the first attempts to walk are terminated by the collapse of the hind limbs or by a fall precipitated by forelimb collapse. The animal progresses through a stage wherein he seeks the support of walls but eventually emerges into the stage of stabilized deficiency. The deficiency of postural tonus and the weakness of muscular contraction are obvious only during the early part of the deficiency period in the animals with total ablation. They may be demonstrated for longer periods of time in the hemidecerebellate animals in which there is opportunity to make comparison with the normal side in the same animal.

The reality of the atonia and asthenia as a sign of cerebellar deficiency was denied by Dusser de Barenne (113, 114). It is possible that this investigator missed the relatively brief period during which it may be demonstrated in the totally decerebellate animal. Dusser de Barenne suggested that atonia and asthenia as described by Luciani were the result of inadvertent damage to the vestibular nuclei. However, intentional damage to the vestibular system produces an entirely different syndrome in the chronic animal. In examining his animals for signs of asthenia or weakness, it is possible that he confused evidences of weakness and fatigability.

In the primate, the evidences of facilitatory withdrawal are more profound and persistent than in the quadruped (9, 123, 188–190, 249). Macaques were unable to stand because of atonia and asthenia for a protracted period after operation. As walking became possible, it was accomplished only with lateral swaying and with frequent pauses during hind limb collapse.

DISORDERS OF PHASIC CONTRACTIONS. As the quadruped gradually compensated for its deficiencies, locomotion improved and the animal developed competence in caring for itself. Full return to normal never occurred after complete removal of the cerebellum and residual deficits remained which manifested themselves most clearly in lack of adequate control of phasic contractions. This was evident for both forms of phasic contraction, whether reflexly or voluntarily induced.

The phasic postural reactions, so carefully and completely examined and defined by Rademaker (277), were found to be altered during the period of stabilized deficiency. The reflex supporting reaction elicitable from tactile and proprioceptive receptors in the feet and toes was exaggerated. The changes of weight-bearing strength which are produced by displacing the body to one side revealed an exaggeration of contralateral inhibition. The hopping reaction, which was lacking early in the recovery period, was delayed and poorly executed during this period. In addition to these postural reflexes, tendon reflexes have been observed to be hyperexcitable for months following complete removal of the cerebellum (182, 183, 335). The reflex status of the totally decerebellate primate has never been reported as the subject of a detailed study.

Perhaps the most dramatic of the permanent deficiencies following total ablation are the deficiencies of control in time and strength of voluntarily-evoked phasic reactions. The various signs which are now called collectively cerebellar ataxia, were first de-

scribed completely by Luciani (188–190) who used the term astasia. All observers since Luciani have described the massive, coarse tremor of the head, neck and shoulders. This tremor was particularly evident when the animal approached a food dish, gradually compensated but never completely disappeared. The inadequacy of timing and direction of movement of limbs which at first made walking impossible gradually improved, but the animal always walked with abducted limbs. In spite of the wide base, poor placement of feet and timing of contractions frequently resulted in swaying for which the animal could compensate only by crossing one leg over the other.

For reasons which still remain unknown, not all types of movement were ataxic. This was confirmed by Dusser de Barenne (113, 114) who was struck by the normality of the scratch reflex, by the lack of disturbance of the movements engaged in by dogs seeking to bite fleas and by the grace of the movements by which cats cleaned their snouts with their forepaws. Because of the ability of the decerebellate animal to perform such complicated movements without ataxia, Dusser de Barenne concluded that the major function of the cerebellum was related to the control of locomotion.

The same evidences of cerebellar ataxia have been described in the primate after total ablation (9, 123, 188–190, 249, 290). Munk (249) described clearly the disturbance of progression in complicated movements, a sign which Holmes (158) later called decomposition of movement.

Unilateral Cerebellar Ablations

Since it had been recognized even prior to Luciani's studies that signs of cerebellar deficiency were most obvious on the ipsilateral side of the body, Luciani considered the use of hemidecerebellation as one of the most valuable experimental maneuvers (188–190). He argued that such an ablation afforded the opportunity to compare a completely normal and a deficient side in the same animal and thus obtain a more sensitive measure of the induced deficiencies. Bremer has pointed out the error of the assumption that the effects of unilateral ablation are completely unilateral (36) by demonstrating the differences between the effects of *a)* splitting and removing one half of the cerebellum, *b)* removing one cerebellar hemisphere only, and *c)* sectioning the cerebellar peduncles of one side. Furthermore, histological changes on the 'intact' side inevitably occurred (301) after lesions which were strictly unilateral in their initial distribution. The crossing of some of the ventral spinocerebellar fibers and the crossed fastigiobulbar fibers were inevitably interrupted by unilateral ablations. Nevertheless, the studies of hemidecerebellation have been of value in confirming and refining the conclusions drawn from the study of the results of total ablation.

SIGNS OF INHIBITORY WITHDRAWAL. It has been generally agreed that the spastic phenomena resulting from release from inhibition occurred on the ipsilateral side of the body (113, 114, 182, 184, 188–190, 278, 290, 335). These were exhibited as pleurothotonus, forelimb rigidity, and rotation of the head, neck and eyes. In the quadruped these abnormalities persisted for approximately one week and then begin to abate. In the primate the signs were essentially similar to those in the dog and cat but less intense and less enduring (29, 123, 182, 188 190).

SIGNS OF FACILITATORY WITHDRAWAL. The hypotonia and weakness of the musculature of the ipsilateral side of the body were more clearly evident after hemidecerebellation by contrast with the contralateral side. During quiet standing, after the abatement of the spasticity, hypotonia was manifest by the gradual sagging of the body to the operated side as the limbs collapsed. The weakness of muscular contraction also became evident during walking through the tendency of the legs to fold. These observations of Luciani (188–190) have been confirmed (290, 335). However, Lewandowsky (182, 183) and Dusser de Barenne (113, 114) were unable to agree with Luciani's designation of some of the signs as asthenia and atonia. The weight-bearing tests devised by Rademaker (277) failed to reveal evidence of atonia and asthenia, but it must be emphasized that the observations were made during the period of stabilized deficiency and therefore could have been too late. Rademaker did, however, make one group of observations which indicates one possible source of the atonia which others observed. With his animals in the supine position, he noted that the forelimb ipsilateral to the lesion was rigidly extended but that the spasticity disappeared upon elicitation of a positive supporting reaction from the contralateral limb. It went unrecognized that these exaggerated effects of contralateral inhibition could contribute to atonia on the affected side when the animal was in the normal standing position. Similar observations were also reported by Simonelli (299) who introduced valuable but

neglected techniques for the detection and analysis of postural and reflex asymmetries.

In the macaque, atonia and muscular weakness have been observed by many (29, 123, 182, 188–190) investigators. The results of unilateral cerebellar and peduncular lesions in a number of primate species (29–31) were reviewed by Fulton & Dow (126) who were struck by the increased intensity and persistence of the atonia and weakness in the chimpanzee as compared to the lower members of the series.

DISORDERS OF PHASIC CONTRACTIONS. The disorders of phasic contractions following unilateral cerebellar ablations were essentially like those following total ablation with the exception that they were confined to the ipsilateral side of the body (36, 111, 113, 114, 182, 183, 188–190, 277, 290, 335). The coarse tremor and oscillations of the head and neck were obvious and dramatic. These movements were best understood as the result of inaccurate control of timing and strength of muscular contraction and inaccurate compensatory movements. Signs of ataxia also were evident in the manner of control of limb position and placement during locomotion. Similar signs appeared in primates subjected to unilateral lesions (29, 123, 182, 188–190). In this form the astasia was more prominent in the limbs than it was in the quadruped, perhaps because the greater range and complexity of movements of the primate limb made the defects more obvious.

Localized Ablations of Portions of Cerebellum

As information about the anatomical relations of the cerebellum grew in amount and reliability, and as the results of stimulation experiments became known, numerous attempts were made to discover some form of localization of function within the cerebellum. Earlier experiments of this type were influenced by Bolk's (27) comparative anatomical studies and consisted of attempts to test his hypotheses concerning somatotopic organization of efferent pathways. Later experiments have been directed more toward testing the anatomical subdivision of the cerebellum into vestibular, spinal and cerebral components as suggested by Ingvar (157, 164, 165, 180). With the growth of information from electrophysiological studies demonstrating somatotopic organization in the spinocerebellar relationships, the ablation experiments have been designed to test these findings as well. The following discussion will consider the results of localized ablations from the point of view of the three major anatomical and functional subdivisions, with attention to somatotopic localization where this has been the major objective of the experiment.

FLOCCULONODULAR LOBE. The many studies of the results of partial cerebellar ablations which were done before anatomical relations were well understood did not add particularly to our knowledge of cerebellar function inasmuch as they involved lesions which overlapped extensively into nonvestibular portions of the cerebellum. More modern attempts to destroy this portion of the cerebellum are by its anatomical inaccessibility also limited to a relatively few studies.

For a few days following unilateral ablations of the nodulus (X) in guinea pigs, the animals exhibited marked dynamic signs consisting of forced circling, rolling, nystagmus, and abnormal head and trunk postures (79, 199). Disturbance of otolithic eye reflexes persisted for a few weeks longer, but eventually compensation was complete. In the same species, lesions confined to the flocculus (H X) failed to produce the dynamic signs but did abolish the otolithic reflex control of eye movement (199). In an extended series of experiments (11) reviewed by Tyler & Bard (341) and confirmed by Wang & Chinn (356–358), the integrity of the nodulus of the dog was found to be necessary for the development of motion sickness. In cats, lesions involving the pyramis, uvula and nodulus (VIII A, VIII B, IX, X) produced disturbances which were comparable to those following destruction of the anterior lobe (67, 68).

The vestibular type of disturbance was apparently seen much more clearly in the primate. In the macaque, baboon and chimpanzee (105) lesions involving the nodulus and lower uvula produced obvious signs of disequilibration without tremor, dysreflexia or atonia. Asymmetrical lesions produced disturbances opposite in laterality to those produced by unilateral labyrinthine lesions. These observations have been confirmed in the macaque (62). Bilateral lesions of the flocculus (62) produced essentially the same signs of disequilibration, but these were less intense and more transient. Destruction of the supramedullary portion of the juxtarestiform body in the macaque (119, 120) resulted in signs which duplicated those produced by flocculonodular lesions (62, 105), including the absence of postural and reflex disturbances. Interruption of the intramedullary portion of the same structure reversed the laterality of the signs, causing them to resemble the results of unilateral labyrinthectomy (119).

ANTERIOR LOBE OF CORPUS CEREBELLI. *Destruction of Cortex.* The results of destruction of the anterior lobe and its efferent paths complemented the results of stimulation of the same structures and revealed that the dynamic signs of release from inhibition were due to encroachment upon this portion of the cerebellum.

Rothmann (288) seems to have been the first to make the association between the anterior lobe and the opisthotonus and extensor rigidity which followed its complete removal. Rothmann also demonstrated that the more caudal portions of the vermis (VI–IX) were responsible in part for the compensation which occurred, for if they were later removed the signs of inhibitory withdrawal were repeated in a more intense and enduring fashion. It is noteworthy, however, that the signs of spasticity were not the sole results of Rothmann's ablations, for his animals demonstrated ataxic gait and tremor in the head and trunk as well. There is general agreement about the validity of Rothmann's findings for the quadruped (24, 67, 185, 313, 339). Snider & Woolsey (313) observed additionally that the spastic manifestations are greatly accentuated by removal of the pericruciate cortex as well, an observation which has been fully confirmed (185).

The situation following anterior lobe (I–V) ablation is not as clear for the primate. Fulton & Connor (125) reported that exaggeration of postural tonus and reflexes and increased tendon reflexes were produced in the macaque (II–V) along with gross disturbances of coordination of the limbs and head movements and tremor. Connor & German (78) uniquely reported opisthotonus in this form. On the other hand, Carrea & Mettler (62) observed no release phenomena in the macaque following incomplete lesions. Soriano & Fulton (314) reported that whereas release phenomena were not observed after anterior lobe ablation in the macaque, this could be made evident in exaggerated and enduring form by subsequent removal of cerebral motor areas. Some of the above observations have been reported only in abstract form without histological studies, but the general mildness of the signs and their short duration recall the results of complete ablation in the macaque (34, 69, 327) and the paucity of inhibitory responses to stimulation of the anterior lobe in the macaque (151, 310).

Further evidence of the inhibitory action of the anterior lobe was obtained from observations of the increase in decerebrate rigidity which follows inactivation of this portion of the cerebellum in the quadruped (32, 45, 58, 59, 105, 196, 236, 262, 299). This change was evident only on the ipsilateral side of the body if the inactivation was unilateral (32, 45, 59).

Earlier attempts to assign somatotopic areas within the anterior lobe were unsuccessful (288). However, Chambers & Sprague (68) noted that lesions confined to the medial portion of the anterior lobe produced the signs of spasticity with extensor rigidity, whereas lesions confined to the intermediate portion resulted in an increase in resting flexor tonus in the forelimb and flexion hypermetria during walking. In a more extended study of the results of discrete cortical lesions in the vermis of the cat (67) these investigators came to the conclusion that each half of the entire medial vermis was involved in the control of postural tonus, locomotor activities and equilibrium for the whole body. The more laterally placed intermediate portions, on the other hand, were thought to be related to ipsilateral postural reflexes and individual movements. They reported somatotopic organization in both portions of the vermis, with more overlap medially than in the intermediate portion. They assigned the tail to the lingula; the hind legs and pelvic girdle to the centralis and rostral culmen; the forelegs, pectoral girdle, head and neck to the caudal culmen; and the head, neck and eyes to the folium and tuber vermis.

Efferent paths. The results of studies of nuclear lesions produced by techniques involving extensive cortical damage were not easily interpretable and will not be dealt with here. With the use of the stereotaxic technique, the cerebellar nuclei may be destroyed with insignificant damage to the cerebellar cortex and are therefore susceptible of interpretation. However, it is important to remember that the crossing fastigiobulbar fibers course through the nucleus of the opposite side, so that it is impossible to produce unilateral signs by unilateral fastigial destruction (169).

Complete destruction of the fastigial nuclei in the intact cat (13, 14, 17, 185) produced signs of release from inhibition without atonia. However, unilateral destruction of the fastigial nucleus in the intact cat (13, 14, 17, 316) produced signs of spasticity contralaterally only, whereas the ipsilateral posture was flexor, and atonia was demonstrable ipsilaterally for several weeks. If, following such lesions, the vermian cortex was removed (316), the laterality of the signs reversed. Batini & Pompeiano (13, 14, 17) report that ipsilateral atonia and contralateral spasticity were also produced if only the anterior half of the nucleus was destroyed. If only the caudal half was

destroyed, extensor tonus appeared ipsilaterally and flexed posture contralaterally.

This situation has been subjected to a more complete analysis in the decerebrate cat. Removal of the anterior lobe cortex was followed by increased rigidity ipsilaterally and flexion contralaterally (66, 316). If the subadjacent fastigius was then destroyed, the rigidity disappeared ipsilaterally and reappeared contralaterally. On the basis of these results, Chambers & Sprague (66, 316) considered that part of the fastigial nucleus was activated by extracerebellar afferents independently of the cerebellar cortex. Moruzzi & Pompeiano (244, 247) have confirmed these results but, utilizing selective destruction of the various portions of the nucleus, have come to a different conclusion. They described ipsilateral fastigial atonia with contralateral increase in tonus which was produced by destruction of the rostral part of the nucleus alone. They also described contralateral fastigial atonia and ipsilateral increase in tonus which was produced by destruction of the caudal part of the nucleus alone. They concluded that the increased extensor tonus is dependent upon facilitatory activity conveyed from the caudal part of the fastigius over crossed fastigiobulbar fibers. When contralateral extensor tonus is deprived of this facilitation by caudal fastigial lesions, inhibition from proprioceptors in the rigid limb and from vestibular sources overbalances other sources of extensor facilitation and the rigidity disappears from the contralateral limb. When both nuclei are destroyed, the extreme spasticity disappears, the contralateral leg is relieved from some of the inhibitory barrage and becomes rigid once more. In another group of experiments, Batini & Pompeiano (15, 18) have destroyed the origins of the crossed fastigiobulbar fibers bilaterally and decerebrated their animals several days later. Destruction of the medial and lateral portions of the anterior end of the nucleus then gave rise, respectively, to decrease and increase of rigidity ipsilaterally, thus confirming the dichotomy of the inhibitory and facilitatory pathways from the anterior lobe revealed by stimulation studies (243, 245, 246).

Spasticity and other signs of release from inhibition have not been observed following section of the individual cerebellar peduncles.

It is apparent from these studies that the disturbances of postural tonus in the animal subjected to cerebellar lesions are not produced in any simple fashion. The discharge of motor neurons in tonic activity is determined by a balance of influences, among which have been identified cerebellar inhibition, cerebellar facilitation and postural reflex activities organized at the spinal cord level interrelating the limbs on the two sides of the body. Consequently, a single alteration of input to the spinal cord system terminating in the motor neuron may set into action such a number of interrelated events that it becomes impossible to identify in any single phrase the nature of the primary event.

POSTERIOR LOBE OF CORPUS CEREBELLI. It will be recalled that, among the signs of cerebellar deficiency, atonia and asthenia were ascribed to loss of facilitation. It will also be recalled that facilitatory influences from the anterior lobe have been demonstrated by stimulation experiments and have been abolished by anterior lobe destruction. The anterior lobe, however, is not the only portion of the cerebellum which might be involved in facilitatory influences to the motor neuron, for it will be remembered that the cerebellar hemispheres have been shown to exert an effect upon the activity of the motor cortex. Thus, with the information from the stimulation and electrophysiological experiments at our disposal, it might be predicted that atonia and asthenia would form part of the picture of deficiencies produced by destruction of the posterior lobe.

Ablations involving most of posterior lobe. It will be recalled that exaggerated postural tonus, hypotonia and disturbances of phasic movement are all signs reported to follow lesions of the anterior and posterior vermis and its efferent paths. Bremer (36) was the first to emphasize the importance of avoiding damage to the vermis in order to reveal the deficits produced by posterior lobe lesions uncomplicated by signs of inhibitory release. Opisthotonus and extensor rigidity were entirely lacking from these animals, thus confirming, in a negative sense, the vermal origin of these elements of the syndrome of cerebellar deficiency. During the deficiency period Bremer's animals exhibited hypotonia, dysmetria, tremor and weakness of cortically-mediated reflexes, all on the ipsilateral side. These signs were all of short duration, presumably because of the rapidity and completeness of organic compensation. In the light of the repeated confirmations of Bremer's findings as a result of partial lesions of the posterior lobe (see below), the completely negative results of Keller *et al.* (172) defy understanding.

The primate exhibits a similar group of signs following posterior lobe lesions (31, 36, 62). In a summary of experiments performed on different species of primates, Fulton & Dow (126) called attention to the in-

creasing gravity and endurance of ataxia and hypotonia as one moves up the primate scale toward man. They also pointed out that more gross disturbances follow bilateral lesions, and that tremor is not an element of the syndrome unless the dentate nuclei are involved.

Partial lesions of posterior lobe. Experiments involving the isolated removal of lobules were clearly directed toward the revelation of such topographical organization as might exist in the posterior lobe.

Several observers have reported cervical ataxia to be the only sign following lesions of simplex (VI, H VI) in dogs (186, 288, 344, 345). In a similar fashion, dysmetria confined to the forelimb has been reported to follow lesions of Crus I of the ansiform lobule (H VII a) and of the hind limb after lesions of Crus II (191, 288, 336, 344, 345) in both dogs and monkeys. These observations have not been confirmed by more recent investigators (100, 121, 283, 284). Carrea & Mettler (62) in macaques and Chambers & Sprague (67) in cats reported that lesions restricted to the cortex of Crus I and Crus II were not productive of symptoms. It was only when the underlying nuclei or the anterior lobe were involved that cerebellar deficiencies were observed.

In the cat (67, 121, 251, 252) and guinea pig (198) ablation of the rostral lamellae of the paramedianus (H VII b), related to the folium and tuber vermis, resulted in ataxia confined to the foreleg. Ablation of the caudal lamellae (H VIII a), related to the pyramis, resulted in ataxic signs confined to the hind leg. None of these observers noted any dynamic signs or disorders of trunk or eye musculature. On the other hand, when all of the paramedianus was removed (67), signs resembling those following ablation of the intermediate portion of the anterior lobe were observed in mild and transient form.

In the guinea pig (198) ablation of the folium and tuber vermis (VII A, VII B) produced signs similar to those seen following removal of the related lamellae of the paramedianus. Chambers & Sprague (67) reported that their cats exhibited increase of extensor tonus, foreleg hypermetria, resting head tremor, and a failure to react to light and sound which was interpreted as being due to inattention.

Results of ablation of the paleocerebellar portion of the posterior lobe have been inconstant. Guinea pigs and macaques were free from deficiencies (62, 105, 198). The dog was reported to exhibit asthenia and ataxia in the hind legs (288). The cat has been said to develop weakness and atonia (322, 323) and to show signs resembling those following removal of the anterior lobe (67).

In an extended study, Di Giorgio and his colleagues have demonstrated that the unilateral ablation of large portions of the posterior lobe produces postural asymmetries which are clearly defined by their techniques of examination (98, 99, 101, 102). These asymmetries disappear immediately following spinal cord transection but reappear with the passing of spinal shock to endure for hours. This residual effect on spinal cord function develops within a few hours following the cerebellar lesion and is not dependent upon afferent supply or cerebrospinal supply to the affected segments of the cord. The observations have been confirmed in the pigeon (197).

Efferent paths of posterior lobe. There are very few studies of the effects of well-controlled lesions of the intermediate and lateral nuclear groups made with techniques which did not also damage large cortical areas.

Snider (302) has reported tremor, ataxia and slight hypotonia ipsilaterally following unilateral destruction of the intermediate nucleus in the rabbit. Chambers & Sprague (67, 68) also destroyed this nucleus in the cat, producing a permanent loss of ipsilateral tactile placing. Their animals also exhibited a sluggishness of ipsilateral proprioceptive placing and of hopping reactions for about one week. Accompanying these signs were a mild increase in extensor tonus and hypermetria in the ipsilateral foreleg.

Lesions of the lateral nuclei in the cat (67) were not productive of any alterations in tone or spinal reflexes, but placing and hopping reactions were depressed and there was noted a poverty of limb movement. Botterell & Fulton (31) reported that neocerebellar decortication in the macaque produced awkwardness, disturbances of gait and hypotonia ipsilaterally. When such lesions were extended to include the lateral nucleus, the ataxia was more severe and a transient tremor appeared. Carrea & Mettler (62) reported intense ataxia and ataxic tremor to follow dentate lesions in macaques.

A syndrome similar to that produced by large posterior lobe lesions followed section of the superior cerebellar peduncle in the macaque (259, 354). This lesion failed to produce any signs of release but produced atonia and ataxia ipsilaterally. The signs abated in approximately 6 weeks but compensation was never quite complete. Bilateral section increased the severity of disturbance of voluntary movement tremendously, brought on kinetic tremor and delayed compensation. Attempts to delineate the portions of the brachium

conjunctivum responsible for the ataxic signs and for the tremor have produced somewhat confusing results (62, 206).

Although section of the inferior cerebellar peduncle has not been reported to give rise to any signs referable to the fastigiobulbar fibers which it contains, its interruption produces deficiencies which are apparently due to its cerebellopetal fiber content. Ipsilateral asthenia, hypotonia and dysmetria of transitory nature are reported to occur in the dog and monkey (25, 118–120). These signs get quantitatively more pronounced without change of quality as the lesion involves the corpus restiformis at higher and higher levels. Turner & German (340) report that disturbances of locomotion followed section of the middle cerebellar peduncle.

Perspective

It will be recalled that the experiments involving electrical recording and the experiments involving stimulation revealed a degree of somatotopic organization of the cerebellar cortex which was somewhat diffuse, showing overlapping fields and indistinct borders. The experiments involving ablation reveal the same sort of picture insofar as the vermis is concerned, with only the paramedian lobule affording good correlation with electrophysiological data.

However vague the somatotopic picture may be as revealed by all methods of study, there are certain correlations which deserve attention. The major influence on postural tonus revealed by stimulation concerns the anterior lobe and the fastigial outflow. The major source of the inhibitory release responsible for the dynamic signs of spasticity following ablation is the anterior lobe and fastigial outflow. This is the area in which are concentrated the terminations of the spinocerebellar afferent systems. On the other hand, the electrophysiological experiments revealed that cerebrocerebellar afferents terminate in the anterior as well as the posterior lobe, thus failing to reveal a differentiation, on this basis, between the paleocerebellum and the neocerebellum. It is perhaps significant that atonia and ataxia as signs of cerebellar deficiency also fail to afford a distinction between the paleocerebellum and neocerebellum since they are associated with lesions in both portions of the organ.

The reader is only too aware that the deficits which follow cerebellar ablation are complex and difficult to understand solely on the basis of the observation and description of the deficits. Real understanding will come only when the details of the mechanisms and the disturbed functions which underly these deficits are better known. Such mechanisms can be revealed only by more sophisticated testing of motor neuron control systems carried out in the presence and in the absence of cerebellar function. Such experiments may be directed toward the question of how the cerebellum affects a given control system. Some experiments of this variety have been carried out but only a start has been made. This sort of information will be briefly reviewed in the following section of this chapter.

MECHANISMS OF CEREBELLAR FUNCTION

Mechanisms of Influence upon Postural Tonus

The tonic discharge of a spinal cord motor neuron represents, at any moment, the integrated result of a multitude of influences which serve to adjust the rate of discharge in such a way as to fulfill the needs of posture. One type of maladjustment of this function may arise (*a*) as a result of an excessive barrage of excitatory impulses driving the motor neurons at a higher frequency, or *b*) as a result of a withdrawal of tonic inhibition, leaving the motor neurons more responsive to excitatory impulses which are then capable of increasing the rate of discharge. Either of these changes would, until compensated, appear as an exaggeration of tonic muscle contraction. Diminution of tonic muscle activity could, of course, also arise in two ways by the reverse of the changes described above.

ORIGINS OF HYPERTONUS. The origins of the hypertonus or spasticity which follows immediately after cerebellar ablation, more obviously in quadrupeds than in primates, are numerous and not fully understood. Even though vestibular reflexes still remain intact (94, 194) after removal of the cerebellum, this is not to say that the vestibular system is not altered in its function. The facilitatory effect of the lateral vestibular nucleus upon tonic activities of the spinal motor neurons has been fully demonstrated (10). It is quite probable that the release of these nuclei from tonic cerebellar inhibition (97) is one of the important sources for the dynamic increase in tonus (184, 266, 318). Further contribution to the overactivity of motor neurons probably originates through a release from inhibition of tonic proprioceptive reflexes originating in neck musculature (12, 16). It is possible that such release is not direct, but secondary to withdrawal of

tonic cerebellar influences on the inhibitory portion of the medullary reticular formation. The importance of differentiating between signs of spasticity dependent upon enhanced gamma efferent firing (134–136, 285) and similar signs dependent upon primary facilitation of alpha efferent discharge has recently been forcefully emphasized (155, 332, 333).

ORIGINS OF HYPOTONIA AND ASTHENIA. It will be recalled that hypotonia is one of the prominent signs of cerebellar ablation in the primates and appears following the abatement of the dynamic signs in the quadrupeds. This alteration in motor neuron behavior also has a complex origin which is not clearly understood. The silencing of the gamma efferent system (135) is one of the final steps which is probably involved, but the intermediate steps have not been revealed. The additive effects of cerebral and cerebellar ablation in producing spasticity (185, 313, 314) certainly point to an inhibitory function on the part of the cerebral cortex, but again the intermediate steps are unknown. The spinal cord itself must certainly be considered as a third probability as an origin of hypotonia. Even in the acute decerebrate preparation, section of the spinal cord at the upper thoracic level will be followed by an augmentation of decerebrate rigidity in the forelimbs—the Schiff-Sherrington phenomenon (318). This inhibitory influence which is furnished by the normal spinal cord may be related to the abatement of the spastic signs and, through its exaggeration, to the subsequent atonia. This probability is supported by recent experiments (12, 16) which differentiate labyrinthine and tonic neck reflex mechanisms involved in the Schiff-Sherrington phenomenon.

Although no clear-cut evidence is available, it has been suggested (36) with reason (281, 282) that asthenia is a manifestation of the withdrawal of a tonic facilitatory action exerted on the cerebral cortex by the cerebellum.

Mechanisms of Influence on Phasic Reflexes

Although no reflex pathways are considered to course through the cerebellum, the possibilities for indirect cerebellar influences on reflexes are numerous because of the number of structures and paths through which the cerebellum might indirectly exert a modulating influence. Modifications of behavior in the gamma efferent system is undoubtedly one of the features of reflex control which must be considered (134). Influences on the brain-stem reticular formation (213) and vestibular nuclei (97) offer other routes for the production of alterations of reflex excitability (300, 301). Even reflexes which are mediated through cerebral cortical function (66, 316) may be secondarily altered by the influence which the cerebellum exerts upon the cerebral cortex (60, 88, 281, 282).

Mechanisms of Influence on Voluntary Movement

It is obvious that every voluntary movement must be initiated from and superimposed upon a background of posture. It follows then that inadequacies of postural control and abnormalities of postural reflexes (300, 301) will be reflected in disturbances of phasic movements induced by voluntary action. However, in addition to this general deficiency of functions which form a foundation for voluntary movement, other, more specific possibilities should be pointed out. It has already been mentioned that these disturbances appear as manifestations of cerebellar dysfunction primarily in the form of tremor, dysmetria and dyscoordination.

Although the brain-stem structures the disturbance of which underlies the genesis of tremor are still in doubt (62, 206), the manifestation of tremor as a disturbance related to cerebral motor function seems well established. Reasoning that tremor was a characteristic of poorly controlled voluntary movement, Fulton *et al.* (127) were led to demonstrate its abolition in the decerebellate cat by decortication. In an extension of this work to the baboon and macaque (9), it was found essential to ablate the entire precentral motor cortex in order to abolish cerebellar tremor. Thus, disruption of the voluntary control system abolished the signs of its disorganized function.

It has been suggested that dysmetria and dyscoordination may have their origin, in part, in the breakdown of functional relationships between gamma and alpha efferent systems (318). This suggestion is supported by the observation that gamma discharge precedes alpha discharge in many forms of muscular contraction (136) and that cerebellar inactivation is followed by a depression of gamma efferent discharge (135). The older idea that a disturbance of reciprocal innervation lay at the heart of these two signs of deficiency has been disproved (264, 337, 338). In the light of evidence of cerebellar modifications of cerebral functions, it is probable that, like tremor, dysmetria and dyscoordination also depend upon inadequacies of organization of the voluntary control mechanisms within the cerebral cortex (36).

Mechanisms of Compensation

It was indicated earlier that Luciani (188–190) expressed his opinion that compensation for cerebellar deficiencies occurred by virtue of the acquisition of new functions by structures not previously involved (organic compensation) and through a process of learning and training which permitted correction of deficits (functional compensation). In terms of the mechanisms involved in these different forms of compensation (if indeed they be different), we know no more than we know about learning and the acquisition of skill in general. Nevertheless, the location of structures involved in the compensation processes has, to a limited degree, been revealed.

It has been repeatedly emphasized (36, 188–190) that if additional cerebellar lesions are made in an animal already compensated, the resulting new deficits exceed in intensity those which would have occurred as a result of the second lesion alone. It would thus appear that the cerebellum itself is involved in the changes occurring during compensation. The role of spinal cord inhibition in the recovery from the dynamic signs and in the precipitation of atonia has already been alluded to (12, 16). The original observations by Luciani (188–190) of the reappearance of deficiency signs in a compensated animal following removal of the cerebral motor cortex have been repeatedly confirmed. Thus, the cerebral cortex must also be involved in the reorganization of the control system which brings about compensation. In addition, it has been demonstrated in the cat that compensation from unilateral fastigial lesions occurs in 14 to 35 days; that compensation following subsequent bilateral motor cortex ablation occurs in 14 to 17 days; and that the compensation following decortication is premesencephalic in its location (12, 16).

CEREBELLAR DEFICIENCIES IN MAN

The emphasis in this chapter has been upon the discussion of cerebellar functions as they are revealed by observations upon experimental animals under conditions that permit an attempt at an experimental analysis. Fundamentally, the signs of cerebellar deficiency in man are like those seen in experimental primates (126) with a more grave disturbance of skilled movement and a more profound and enduring hypotonia. No attempt will be made to describe the cerebellar syndrome in man, the reader being referred to the excellent discussions of Holmes (158, 159), Goldstein (133), Bremer (36) and Moruzzi & Dow (241). It should be remembered that *a*) in man cerebellar disease or injury rarely respects anatomical boundaries and *b*) the signs of slowly developing cerebellar lesions are mitigated and sometimes obscured by concurrent compensation.

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CHAPTER LII

The reticular formation

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CHAPTER CONTENTS

PERHAPS IT IS WELL TO REMEMBER from time to time that the living organism from ameba to man is a single unit and not a collection of systems. These organisms, regardless of station in the phylogenetic scale, must react successfully to surrounding environments if they are to continue to exist. In the simplest orders, no nervous system is necessary but, with developing complexity of structure and function, a system is appended for relating to each other the several living processes. This appendage in man is a highly prosencephalized brain; and in order to unify the individual activities of its 10 billion neurons into appropriate patterns of functions, systems of control have developed.

It now appears likely that the brain-stem reticular formation represents one of the more important integrating structures if not, indeed, the master control mechanism in the central nervous system. Neuron combinations here long have been known to mediate the control of many visceral functions such as respiration, vasomotor tone and gastrointestinal secretion, and in recent years investigations have indicated participation of this region in neural processes subserving temperature regulation and neuroendocrine control. Furthermore, information has been adduced recently which assigns to the reticular formation a major role in the mediation of three more general neural functions. First, it is known to be implicated in the arousal response and wakefulness. Second, it exerts a critical degree of influence over motor functions concerned in phasic and tonic muscular control. Third, the central brain stem is capable of modifying the reception, conduction and integration of all sensory signals to the degree that some will be perceived and others rejected by the nervous system. This chapter will ex-

plore the physiological processes by which the reticular formation contributes concurrently to the mediation of these diverse attributes of central nervous system function.

ANATOMICAL CONSIDERATIONS

According to Allen (8), the 'formatio reticularis' is embryologically that mass of cells in the brain stem and spinal cord which is not utilized in the formation or motor root or sensory relay nuclei. Phylogenetically it is very old, and in organisms of primitive phyla it represents the bulk of the entire central nervous system. In higher vertebrates, however, in which the process of encephalization is highly developed, only a relatively small amount of reticular formation remains in the spinal cord but that portion which occupies the central brain stem from medulla to thalamus assumes a mass of considerable proportions. Presumably, the reticular formation expands in higher orders as a result of the development of cerebral and cerebellar hemispheres with which it is closely related functionally (169).

Allen observes further that in its development, the reticular formation surrounds or partially surrounds the sensory nuclei of the thalamus and that such structures as the nucleus ruber, substantia nigra and other differentiated hypothalamic and midbrain nuclei should be considered probably as specialized derivatives of it. Clearly, then, considered developmentally, the reticular formation is closely related caudally to collections of neurons in the gray substance of the spinal cord, presumably internuncial (169), and cephalically to subcortical nuclei in the forebrain such as the sub- and hypothalamic portions of the thalamus and perhaps even the septal region (1).

The reticular formation proper begins, according to Ramón y Cajal (222), in the bulb a little above the decussation of the pyramids. It is centrally located, being surrounded everywhere by a shell of neural tissue consisting of long fiber tracts and nuclei of specific conduction systems. Throughout this centrally located area, collections of cells alternate with regions which appear grossly as nuclei; Olszewski (207) in an extensive study has described 98 such masses in the reticular formation. A detailed discussion of the cytoarchitectural structure of this region, however, would be pointless here as these collections of cells do not appear in general to represent functional units. Rather, as will be discussed later, the physiological characteristics exhibited by the reticular formation appear largely to be independent of visible structural relationships.

Reticulopetal Connections

An important source of neurons connecting with the reticular formation is known to be the spinal cord. These connections or collateral branches leave the main axon trunks of the medial lemniscus, and spinothalamic or spinocerebellar tracts as they course through the brain stem. Ramón y Cajal describes such collaterals in great detail and Allen confirms their presence. Additionally, it may be that there are cells in the spinal cord which send axons directly to the reticular formation, as suggested by Probst (219) and confirmed recently by Collins & O'Leary (56) by Brodal (40) and by Nauta (202). It is likely such direct fibers travel in or near long funiculi in ventrolateral and dorsal segments of the spinal cord. Whether by collateral or direct connection, these spinoreticular pathways have been repeatedly described anatomically and are known to be quite prevalent (22, 40, 193, 194).

Spinoreticular axons appear to enter the reticular formation throughout the longitudinal extent of the brain stem (8, 221), although there may be areas which are particularly heavily populated with these reticulopetal fibers. Morin (193) suggests that they are particularly dense in the medullary region, but it is clear that the reticular formation receives connections from the spinal cord throughout its length.

The reticular formation receives afferent fibers from other structures in the brain stem as well as from the long tract systems. Ramón y Cajal described anatomical connections with the principle sensory nuclei, with interstitial motor cells of the bulb and with the quadrigeminal bodies. Recently, also, on the basis of Golgi studies, Scheibel (238) has confirmed these observations. In addition, he describes the extremely wide area which the dendrites of single reticular neurons are capable of covering. This anatomical structure of reticular neurons suggests that they receive synaptic contact from laterally located pathways and nuclei through these remarkable dendrite extensions as well as by central convergence of collateral axons from projection systems.

Corticifugal fibers, another source of reticulopetal axons, are known to originate in the frontal convexity (134, 152, 181, 187, 230), sensorimotor cortex (177, 222), particularly in the motor region (230), and cingulate gyrus (230, 280). Axons destined for the

reticular formation also arise in the parietal (182), lateral temporal (183), orbital (275) and paraoccipital (58, 180) areas, but these regions were found to be relatively poor sources of such fibers (230). Recently, Adey *et al.* (2) have demonstrated important reticular connections from rhinencephalic structures, principally the hippocampus and entorhinal region.

Some of these corticoreticular fibers travel in the corticospinal and corticobulbar tracts en route to the reticular formation (222). Ramón y Cajal (222) found them leaving the pyramid in particularly large numbers above the olives at the level of the facial nucleus. Rossi & Brodal (230) describe similar dense collections of corticifugal fibers ending in two well-circumscribed areas; one of these zones was located in the lateral pontine tegmentum and the other resided in the medulla near Olszewski's nucleus reticularis gigantocellularis. Other routes exist through which cortical neurons reach the reticular formation, but probably because these fiber connections are diffuse anatomical evidence concerning them is meager.

An important anatomical and functional relationship is known to exist between the reticular formation proper and the mid-line and intralaminar nuclei of the thalamus, these latter structures being considered the cephalic portion of the reticular system. Most of the data indicating that these thalamic structures receive important direct contact from afferent or corticofugal neurons, however, stems from physiologic rather than anatomic study; at least fiber degenerations have not been described in these nuclei after cortical excisions as they have in the reticular formation itself unless portions of the rhinencephalon were included in the decortication (92, 201). Rhinencephalic links with the thalamus and reticular formation have been followed from the hippocampus to the intralaminar thalamic nuclei (201) and through the fornix into the midbrain tegmentum (92). Adey *et al.* (2) found connections between the entorhinal cortex and reticular formation, and Nauta (201) described reticulopetal axons from the septal region.

Anatomical connections between the basal ganglia and the central brain stem have not been reported, although a major portion of pallidal outflow is known to enter the ventralis lateralis (208), the ventralis anterior or both (223). However, important reticulopetal fiber tracts are known to emanate from the cerebellum. In 1924, Allen (7) reported that neurons in the fastigial nuclei sent axons to the reticular formation and Rasmussen (224) later confirmed this finding. Recently Sprague *et al.* (259) and others (179, 268) have described important bilateral connections between vermal fastigial structures and the reticular formation and intralaminar thalamic nuclei.

Central Brain Stem

Ramón y Cajal was struck by the marked variability in size of neurons in the reticular formation, some being only 12 to 14 μ in the longest diameter, while others were as large as 90 μ. Presumably, then, if soma size relates to axon length, the reticular formation is constructed in a manner which permits conduction both in relatively short steps and in long strides. The soma size can be related further to axon diameter and conduction velocity; hence, both slowly and rapidly conducting elements are present. Also, Ramón y Cajal noted that axons often crossed the mid-line and ramified in all directions both ipsi- and contralaterally. Recently, the Scheibels (239, 240) have confirmed and extended these observations of Ramón y Cajal by describing axons which divide, sending one branch cephalad and one caudad. Each branch subsequently delivers itself of a myriad of collaterals which appear capable of extending long distances. This organizational pattern suggests strongly that a single reticular cell may be capable of exerting its influence both upwards towards the brain and downwards into the spinal cord. It suggests further that these influences may be exerted bilaterally, that they may be conducted rapidly or slowly and that they may be extended widely through the large number of collaterals they exhibit.

Anatomical connections from the reticular formation to the centrum medianum nucleus of the thalamus and to the subthalamus have been described by Lewandowsky (153). More recently, the observations of Russell & Johnson (234), of Papez (209) and of Whitlock & Schreiner (285) indicate that cephalic conduction occurs in relatively well-marked fiber bundles called the lateral reticulothalamic, tegmental and tectothalamic tracts to the mid-line and intralaminar nuclei of the thalamus (285). Brodal & Rossi (42) found that cells projecting cephalically were scattered throughout the reticular formation but were abundant in its medial two-thirds, particularly at the level of the rostral third of the inferior olive and at the level of the abducens nerve. Doubtless, important cephalic conduction is mediated by multisynaptic neuron systems scattered throughout the central brain stem from this diffusion of reticular cells.

Reticulofugal Projections

It is not clear anatomically how influences from the thalamic reticular system reach the cortex, for essentially complete decortication results in no retrograde change in the intralaminar nuclei (217, 218, 274). Contrastingly, cells in the reticular nuclei of the thalamus (along with appropriate relay and association nuclei) do degenerate after cortical resection (53, 228, 229), and one proposal holds that reticulothalamic influences upon the cortex are mediated through the reticular nuclei of the thalamus (125, 126). In addition to a thalamic route, fibers have been described recently which course cephalically from the reticular formation in a region ventrolateral to the thalamus (42, 202, 239, 295), hence it is likely that direct reticulocortical connections exist.

It has been demonstrated that mid-line and intralaminar nuclei degenerate if certain telencephalic structures are destroyed. Rose & Woolsey (229) found intralaminar degeneration only if they destroyed the rhinencephalon, striatum and amygdala in the rabbit, and Powell & Cowan (218) reported similar results by ablating the lateral preoptic area and adjacent parts of the striatum and pallidum. It appears, therefore, that an intimate anatomical relationship exists between the central brain stem and either the paleocortex or perhaps, the basal ganglia or both, as suggested by Droogleever-Fortuyn (65). Connections with the neocortex are somewhat less direct.

Another important projection system of the reticular formation is directed into the cerebellum. According to Brodal (41) and Brodal & Torvik (43), a large collection of cells in the medullary reticular formation (called the paramedian reticular nucleus) send fibers to the anterior lobe, pyramis, uvula and possibly the fastigial nucleus.

ASCENDING INFLUENCES

In 1935 Bremer noted that transection of the brain stem of animals at the collicular level (*cerveau isolé*) resulted in behavioral and EEG manifestations of sleep attributed, he correctly suggested, to deafferentation of the cortex (33). Later developments indicated, however, that the coma exhibited did not depend upon the total elimination of sensory information from cerebral structures, for it was known that responses could be recorded in primary receptive areas of the cortex even when animals were anesthetized. The observations of Moruzzi & Magoun (198) clarified the matter by showing that afferent influx transported centrally through the brain stem was implicated in the arousal mechanism. Clearly, therefore, the coma of *cerveau isolé* animals was shown to depend upon exclusion from higher structures of 'activating' stimuli conducted selectively through this median zone rather than upon the blockade of primary sensory signals transported to the cortex through the lateral brain stem. The area implicated in conveying such 'arousing' information to the brain was occupied principally by the reticular formation and related thalamic nuclei; hence these structures became known as the 'reticular activating system' or RAS.

Electrophysiological Characteristics

EVOKED POTENTIALS: SENSORY CONNECTIONS. In 1936 Derbyshire *et al.* (63) called attention to impulses with long latency elicited by stimulation of the sciatic nerve which could be recorded in surface areas remote from the sensory cortex and hence were distinct from signals conducted in the primary sensory pathways. Subsequently, Dempsey *et al.* (62) determined that this response, called by Forbes & Morison (77) the 'secondary' as opposed to the 'primary' lemniscal response, was conducted through the brain stem in an area central to the medial lemniscus. Since that time, evoked potentials have been recorded in the reticular formation from excitation of somatic sensory (85, 263), proprioceptive (61), sympathetic (85), vagal (59), auditory (85, 263), visual (59, 85) and olfactory (59) receptive or conductive system.

These potentials have been recorded throughout the reticular formation and areas related to it, such as the central grey substance, sub- and hypothalamus, and medial and intralaminar thalamic nuclei (85, 263). More recently sensory signals have been recorded even farther forward in the septal region (2). In general, the extent of the central brain stem over which potentials of each of the aforementioned modalities of sensation can be evoked is common for all (85, 263). Thus, a single electrode placed within the reticular formation can record responses from stimuli applied to a variety of conductor or receptor systems, for example, from stimulation of the sciatic, the sympathetic and the radial nerves as well as from an audible click. While this convergence is extensive it is not absolute, for in practice potentials may be evoked more readily from excitation of some conductive systems than others, and species differences may contribute as well

to the variability in responses exhibited. There is recent indication that the 'significance' of the afferent signal may influence its tendency to evoke reticular discharge (John, R., personal communication).

EVOKED POTENTIALS: CORTICIFUGAL CONNECTIONS. Following early descriptions by Bremer & Terzuolo (39), it was found that potentials also can be evoked throughout the extent of RAS by single shocks applied to each of a number of loci in the cortex (79, 127). These loci in the monkey are found to occupy discrete, circumscribed cortical areas located in the frontal oculomotor fields, sensorimotor cortex, cingulate gyrus, orbitofrontal surface, temporal tip, first temporal gyrus and the paraoccipital region (79). Recently, Adey *et al.* (4) have demonstrated that potentials can be evoked in the RAS also by stimulation of the entorhinal cortex; Green & Adey (104) recorded similar responses from excitation of the hippocampus. Potentials evoked by cortical excitation exhibited the same high degree of convergence which characterized responses of peripheral sensory origin (39, 79). Moreover, convergence within the RAS was extended to include corticifugal as well as sensory inputs, for the same electrode placed in the reticular activating system recorded potentials elicited by pulses applied to afferent conducting systems and active cortical loci alike.

Many of the active cortical loci described were found to funnel into a common pathway by which they are connected to the RAS, as Gunn *et al.* (106) and Eliasson (72) were able to record evoked potentials in the septal region from excitation of many activating cortical zones. Alternatively, some cortical loci exhibit individual connecting routes with the RAS. For example, neurons from the central and premotor gyrus were found to accompany the pyramidal tract (172, 177) to bulbar levels where they entered the RAS and the entorhinal cortex connected with the thalamic and reticular brain stem via the stria medularis (4).

EVOKED POTENTIALS: CEREBELLUM AND BASAL GANGLIA. Evoked potential studies show that the RAS receives important connections from the cerebellum (195, 252, 255). Additionally, central brain-stem responses can be recorded from shocks applied to the basal ganglia (258).

EVOKED POTENTIALS: NEURONOGRAPHY. Connections between cerebral structures and the RAS were thought to be pauci- or, perhaps, monosynaptic (79) as tetanus waves elicited in many of the active cortical loci by the local application of strychnine solution were recorded in the central brain stem (physiological neuronography) (67). Such connections were reported from prefrontal (283), cingulate (204, 280), orbital (235), precentral (177), parietal (Kaufman, A., D. Hansen & T. Shaw, unpublished observations), occipital (178) and temporal (5) regions. It probably is not essential for structures capable of energizing the RAS to display as intimate a relationship with the brain stem as indicated by these neuronographic studies, however. At least, important influences are known to be exerted by the multisynaptic spinoreticular system, and the rhinencephalon may well have devious as well as direct contacts with the RAS (2).

EVOKED POTENTIALS: CONDUCTION RATES. Potentials evoked in the central brain stem by peripheral nerve or receptor excitation display latencies which are somewhat longer than are those recorded more laterally in primary conductive systems (83). Responses evoked by sciatic stimulation exhibited latencies of 12 to 18 msec. in the RAS as compared with 6 to 9 msec. in the medial lemniscus at the same level. Auditory potentials were even more slowly conducted, requiring an elapsed time of 9 to 11 msec. to traverse the distance from receptor to lateral lemniscus and 16 to 20 msec. to reach the RAS. Cortically-elicited responses exhibited comparable or even longer conduction times. Latencies from frontal oculomotor fields were found to be 6 to 12 msec. and similar results were obtained from other neocortical (79) as well as rhinencephalic (4) structures. Impulses are transported, therefore, from the sciatic to the RAS at the rate of about 17 to 30 m per sec. and from the cortex to the RAS with a speed of 3.5 to 6.5 m per sec. Conduction within the reticular formation itself is even slower, occurring at a rate of only 1.5 to 3 m per sec (83). Such slow transport of potentials within the RAS has led to the conclusion that short chain neuron systems must be involved in reticular conduction (169).

Conduction time from the sciatic and other peripheral stimulus sites did not vary significantly when measured to caudal or thalamic portions of the reticular systems (83). Similarly, little variation was noted between the cortex and various recording sites throughout the extent of the RAS (79). These observations prompted the conclusion that the principle delay in reticular as compared to lemniscal potentials occurred in the centrally located structure itself.

Rapid conduction occurred from the sciatic to the brain stem where discharges entered the reticular

formation throughout its extent by means of a brushwork of collateral fibers. Subsequently, repeated synaptic delays intervened to retard the conduction of the impulse markedly. A comparable time-sequence was encountered in studying other reticular inputs.

All stimulus transmission within the RAS is not conducted at such slow rates, however, as occasionally fairly short latency responses are evoked in the cephalic brain stem on stimulation of the medullary reticular formation. It is probable that such responses are recorded in fiber collections such as the central tegmental tract (162), hence that rapid as well as slow cephalic transportation of impulses is characteristic of the RAS.

Another distinction between potentials evoked in 'primary' and in 'secondary' sensory systems relates to the wave form exhibited by each. Lemniscal responses as recorded upon a cathode ray oscilloscope exhibit a sharp, spike-like initial deflection lasting 8 to 12 msec. followed by a wave of longer duration and frequently opposite polarity (83). By contrast, in centrally-evoked responses, the initial short-duration spike-like discharge is lacking, the potential appearing as a high-amplitude wave of long duration. Potentials evoked in the RAS from cortical stimulation exhibited comparable appearances to these discharges of peripheral origin. The wave-like form and long time course of evoked reticular activity suggests, in the light of recent work, that dendrite potentials may be prominently involved (54, 220). The absence of recruitment is not in favor of this possibility, however.

EVOKED POTENTIALS: REPETITIVE STIMULI. Significant differences between the electrophysiological characteristics of RAS and primary sensory pathways was exhibited by responses resulting from multiple shock stimuli. Paired or multiple shocks applied to peripheral nerve or receptor systems at 37 msec. intervals evoked serial volleys in the appropriate primary brain-stem pathway for as long as the pulses continued, the second and succeeding responses being only modestly attenuated. By contrast, in the RAS the second pulse was diminished in amplitude and succeeding responses eliminated when stimuli were separated by as long as 92 msec. (83). Comparable attenuation was encountered when the second of a pair of shocks was applied to a source different from the first (38, 39, 83). For example, a click response was occluded if elicitation was attempted 13 msec. or a cortical response 10 msec. after a potential was evoked in RAS by sciatic stimulation (79, 83). In addition, Bremer & Terzuolo (38) first were able to demonstrate facilitatory as well as blocking interaction between potentials evoked by stimulation of two receptors in rapid succession. The long recovery time appears to be a function of the multisynaptic organization of the RAS. Moreover, the reticular system cells will react to a great variety of inputs, whereas specific conduction pathways and nuclei are sensitive only to signals of one modality.

MICROELECTRODE STUDIES. Knowledge concerning the function of the reticular formation has been greatly advanced in recent years by the wealth of information which has become available concerning the responses by single cells within it (9, 10, 90, 111, 192, 241, 270–272). This material has been beautifully epitomized and interpreted by Moruzzi in symposia on the subject (196, 197). In general, the results of these investigations can be said to confirm and extend those of earlier macroelectrode studies.

A variety of resting rhythms in reticular cells have been described which are characterized by low frequency firing (2 to 5 per sec.), more rapid sustained discharge (50 to 100 per sec.) or intermittent spiking (10, 197). These characteristic discharges have been shown to be altered by potentials reaching the unit from a variety of stimulus sites. The firing rate was augmented on some occasions while at other times it became inhibited (10, 241). That existing conditions of excitability in stimulus and recording site influenced the response to some degree was indicated by the fact that, at different times, a stimulus induced both augmentory and inhibitory responses in a single unit (272). However, true and consistent reversal in reaction of a single cell was demonstrated by Gernandt & Thulin (95). They found that firing of a unit was augmented by vestibular stimulation induced by turning the head in one direction while inhibition followed reverse vestibular excitation. Also, a single stimulus was found to increase the activity of some units and decrease the firing of others (241). Responses such as these appeared to be quite consistent, suggesting to Scheibel *et al.* (241) that characteristic patterns of firing were exhibited by individual neurons of the RAS.

Responses have been elicited in reticular cells by stimuli applied to nerves or receptors of somatic sensory (10, 90, 111, 241, 270), vestibular (95), auditory (111, 241), visual (75), neocortical (usually in or near motor cortex) (111, 272) and cerebellar (45, 90, 272) structures. The cerebellar vermis was more responsive to positive polarization than to single shocks (45).

Single pulse excitation of a stimulus source would usually suffice to elicit a response, although increasing numbers of units were recruited following iterative pulses (111). Convergence of impulses upon a single unit initiated by stimulating several sources (9, 241, 270) was comparable to that demonstrated by macroelectrode techniques. This convergence was prominent but not absolute (10, 111, 241). These results confirm evidence which indicates that the reticular formation is a system of neurons responsive to diverse rather than specific stimuli. They suggest, moreover, that some organization of response to complex stimuli may occur in the RAS as well as in primary systems.

CEPHALIC CONDUCTION OF RAS INFLUENCE. The reticular activating system consists of a caudally-located reticular portion and a rostral thalamic portion. While EEG and behavioral arousal elicited from rostral and caudal RAS appear identical, the two zones exhibit differences in responsiveness to slow frequency stimulation, divergent sensitivity to drugs and contrasting influences upon spinal structures. The thalamic segment will be discussed in detail in a separate review and will be mentioned here only briefly.

Anatomical evidence has indicated that cells in the reticular formation connect with mid-line and intralaminar nuclei of the thalamus which suggests that reticular influence upon the cortex is mediated at least in part by a thalamic relay (42, 285). Reticular neurons which by-pass the thalamus also have been demonstrated, thus an additional or alternative route through which reticular influences could reach the cortex appears to be at least potentially available (202, 239, 285). The existence of these dual pathways has been verified physiologically (263), although it is not possible at present to assess the degree of independence each is capable of displaying in mediating arousal.

Single-shock pulses applied to both caudal and cephalic portions of the RAS evoke widespread cortical responses which have similar wave forms and long time courses. Such responses appear to be comparable to 'synaptic' potentials in the spinal cord (69), hence represent fluctuation in the excitatory state of large neuron populations (52, 54, 154, 157, 220). Cephalically oriented influences of reticulothalamic structures, therefore, seem to be comparable in nature to caudally-directed effects where similar slow potential shifts are known to modify unit discharges in motor neurons (150, 151, 266).

Wakefulness and Sleep

As its structural organization would indicate, the RAS, when stimulated directly or through any of its principle inputs, is capable of initiating widespread alteration of electrical activity in cephalically-oriented cerebral structures. These modifications in the EEG clearly have functional implications, the most important of which relates to the state of awareness exhibited by the subject. Slow wave activity such as spindle-bursting and recruiting have features resembling the tracing of sleep, while low-voltage fast activity induced by repetitive reticular excitation parallels the appearance of the wakeful tracing. It becomes necessary, therefore, to examine behavioral responses which result from experimental stimulations of the RAS and relate them to electrical alterations. (Chapter LXIV by Lindsley in this *Handbook* may also be consulted concerning consciousness and sleep.)

AROUSAL RESPONSE. The concept of a mesodiencephalic sleep regulating mechanism is an old one (175). Early experimental observations by Hess suggested that a sleep center existed. He was able to induce delayed somnolence in chronically prepared animals by prolonged excitation in the region of the mid-line thalamus, presumably the diffusely projecting thalamic nuclei. Subsequently, a contrasting proposal was made which suggested that initiation of wakefulness, not sleep, was the function of the brain-stem centers (191). The electrocortical events characterizing wakefulness were elicited by hypothalamic excitation (199), and behavioral changes suggesting arousal (251) were induced by cortical stimulation. However, Moruzzi & Magoun (198) first recognized that the process of arousal depended upon excitation of the central brain stem and elaborated the physiological mechanism responsible for it.

It has subsequently been demonstrated that EEG arousal results from excitation of the RAS or any of its principle inputs, and rapidly repetitive pulses are found to be most effective for this purpose. EEG desynchronization has been induced by appropriate excitation of the same nerves or receptors which, when stimulated with single shocks, induce responses in the reticular formation. More specifically, EEG arousal in animals immobilized by cervical cord section (*encéphale isolé* of Bremer) or curare has been induced by stimulation of peripheral nerves (85, 263), auditory receptors (85, 105, 263), olfactory system (34, 59, 105), sympathetic nerves (85) and vagi (59, 286). Comparable effects can also be elicited by stimula-

tion of active cortical loci (39, 79, 245), fastigial nuclei (198) and caudate nucleus (247).

Behavior arousal can be assessed in acute experiments when the animal is capable of moving or in chronic preparations in which electrodes have been implanted in appropriate structures. Employing the latter procedure, Segundo *et al.* (244) were able to induce immediate arousal in sleeping animals upon applying short low-voltage bursts to active cortical loci and to the reticular system. Awakening occurred without any suggestion that it was secondary to pain or movement. Concurrent EEG recording showed appropriate transition from the synchrony of sleep to the desynchrony of wakefulness. By contrast, stimulation of other regions failed to evoke wakefulness even though much stronger excitation was employed.

The sleep-inducing responses reported by Hess (115) presumably are elicited by driving the thalamic portion of the reticular system at a rate comparable to slow the EEG frequencies observed during sleep. That such is the case is suggested by the findings of Akimoto *et al.* (6) who were able to induce sleep in dogs by stimulating the diffuse thalamic projection system with 5 cps pulses, while 30 to 90 cps bursts to the same region awakened the animals. This evidence, together with that demonstrating that thalamically-induced recruiting is obliterated during EEG arousal (198), supports the suggestion that rhythms subserving both wakefulness and sleep are mediated by common neural pathways.

There is no doubt that the entire central brain stem from the medulla to the diencephalon participates in the arousal reaction since the response can be elicited from the reticular formation (85, 244), thalamus (85, 244) and septal region (105). In addition, transient arousal is possible even in animals decerebrated at the intercollicular level upon the application of olfactory stimulation (13, 34, 37). The activating function of the more cephalic portions of the system, however, appears to require the energizing influence of its caudal segment (37) since medullary transection does not induce coma (158, 159) while mesencephalic decerebration does (33, 158, 159). Moreover, increasing the size of chronic lesions in the RAS induces progressively deepening stupor (81, 159), and comparable interference with these mechanisms in man elicits prolonged or permanent coma (48, 78, 128). By contrast, experimental lesions in the lateral sensory tracts do not induce apparent alternation in the wakeful state (158).

The RAS is capable, probably, of some spontaneous or autochthonous discharge (37, 59, 196) although, certainly, the bulk of its tonic potency is derived from its several inputs. However, some receptor systems exert a more powerful excitatory influence upon the RAS than do others. Stimulation of the visual nerves has been found to be least effective (13) and somatic sensory excitation most potent in this regard (85). In the *encéphale isolé* where sensation is retained only from the head, relatively normal wakefulness is exhibited (33). In such preparations destruction of olfactory, visual, acoustic, vestibular or vagal afferent inputs does not interfere with arousal while bilateral destruction of the gasserian ganglia abolishes wakefulness (227, 231). Moreover, in truncation experiments, the capacity to arouse is retained until the transection is made rostral to the trigeminal nucleus at which time the sleep-state of the *cerveau isolé* is induced. Clearly, therefore, somatic sensibility from the head is a more powerful contributor to tonic reticular excitation than are all other input systems.

PROLONGED WAKEFULNESS. While the brain-stem reticular system is a critical structure in the mechanism of arousal, it has no intrinsic capacity to induce or sustain wakefulness when separated from higher structures (78). The activity generated within the reticular system must be exerted upon thalamodiencephalic centers, and through them upon the cortex, in order for the alert state to be displayed. Destruction of any portion of this system, the RAS, its thalamic transport or its cortical terminus, render wakefulness impossible or seriously distorted (78).

Reference is made repeatedly in this review to active cortical loci which, when stimulated, elicit arousal (38, 39, 79). It has been proposed that such loci contribute to this process of arousal by functioning in the maintenance of prolongation of sensory-induced awakening (78). It is true that decorticate animals and man exhibit transient brief periods of apparent wakefulness but during such temporary arousal, alertness or appropriate reaction to environment is impossible. It appears, therefore, that crude arousal is possible without cortical contribution but, certainly, the intact cortex is essential for prolonged sustained alert wakefulness characteristic of the normal adult subject.

Neurohumoral Reticular Mechanisms

The influences of metabolic substances, humoral agents, drugs and circulating homones upon arousal mechanisms mediated by the reticular system have attracted much attention recently (24, 26, 28, 30,

60, 123, 124). The critical contributions such substances make to visceral mechanisms are well established. Chemoreceptors in great vessels and brain mechanisms regulating respiratory and cardiovascular phenomena have long been recognized to be sensitive to variations in circulating carbon dioxide. Only lately, however, has it been recognized that this metabolite exerts a prominent stimulating effect upon the reticular formation (60) and an enhancing effect upon cerebral circulation (124). That the influence is direct rather than reflex is indicated by the observations of von Euler & Soderberg (273) who noted that vigorous discharge was elicited in units of the deafferentiated caudal brain stem by ventilating the animals with 6.5 per cent carbon dioxide. Moreover, Dell (60) described augmented firing in reticular units of a brain stem completely isolated by transections at the postmammillary and pretrigeminal levels, and presumably this metabolic excitation is exerted upon the entire reticular formation. By contrast, oxygen was found to have an inhibiting effect upon the reticular formation and this influence appeared to be mediated exclusively through carotid body reflexes (60).

The role of epinephrine and of acetylcholine has long been studied in the peripheral autonomic system, but adrenergic and cholinergic mechanisms have only recently been found to participate importantly in functions subserved by the reticular formation. It has been demonstrated that EEG arousal can be induced by administrations both of acetylcholine and cholinergic and anticholinesterase drugs (26, 28, 60) and of epinephrine as well as adrenergic drugs (24, 26–28, 60). The fact that adrenergic and cholinergic substances both excite the reticular formation has led Rothballer to suggest that separate brain-stem mechanisms respond to each agent (232) and Vogt has been able to find epinephrine and acetylcholine in differential amounts at various loci in the neuraxis (269). These agents appear to act directly upon the reticular formation (24, 60) as well as upon structures representing more cephalic extensions of it, for Porter has described EEG activation of the posterior hypothalamus in response to circulating epinephrine (216). Moreover, Sawyer has reported that anticholinergic and antiadrenergic agents each block neurogenic stimulation of the release of pituitary gonadotrophic hormone (236).

There can be little doubt that these neurohumors act directly upon reticular systems and hence upon structures which are activated alternatively or additionally through neural pathways. Reticular unit discharges have been induced equivalently by injections of epinephrine, by hypoxia (through the carotid chemoceptor reflex) and by stimulation of the lingual nerve (60), indicating convergence from both neural and humoral sources. Arousal of the EEG evoked by neurohumors is the consequence of their action upon the brain stem rather than the cortex, for desynchronization to epinephrine does not occur in animals with intercollicular decerebration (60). Bonvallet *et al.* (24) suggest that arousal to noxious stimuli has a dual source: the initial rapid desynchronization is thought to be mediated by neural excitation of the reticular formation, while slower epinephrine activation serves to perpetuate arousal. Thus, reticular stimulation by either neural or humoral agencies is capable of inducing cortical activation through common reticulocortical pathways. Perhaps such corticipetal conduction can itself be mediated by humoral mechanisms for, following reticular formation stimulation, Ingvar has observed EEG desynchronization in the cortex completely isolated from the rest of the brain. Caudally-oriented reticular formation influences are equally sensitive to humoral excitation, for Dell has shown that the myotatic reflex in decerebrate animals is facilitated by epinephrine administration and inhibited by carotid sinus stimulation (60). Also Sigg *et al.* (248) demonstrated that adrenal medullary substances can excite or inhibit cortically induced movement through action on the reticular formation. Clearly, then, these dual excitatory influences must compliment each other in eliciting all of the responses which result from reticular formation activation.

Drug Effects

ANESTHESIA. When the reticular formation is destroyed or injured either in animal or in man, the subject is rendered comatose, insensitive to stimuli and, except for reflex responses, immobile (76, 78, 81). Because the administration of anesthetic agents induces such behavioral changes reversibly, it might be presumed that these drugs exert a selective effect upon the reticular formation. In general, available information has shown this postulate to be true, although depressant drugs are known to affect other neural regions as well as the central brain stem.

Evidence has been presented by Larrabee & Posternak (145) and reviewed extensively by Brazier (31) which indicates that anesthetic agents exert a blocking effect upon synaptic transmission to a much greater extent than upon nerve fiber conduction

(109). The reticular formation is known to be a multineuronal system as compared to the paucisynaptic direct sensory pathways, therefore, the former region would appear to be far more susceptible to these drugs than the latter.

The selective susceptibility to anesthesia of such polysynaptic systems as the RAS has been emphasized in the past (12, 80, 84). It was demonstrated, for example, that potentials evoked in the reticular formation were completely blocked following the administration of ether, barbital and other central nervous system depressants. By contrast, responses to the same stimuli persisted or were even enhanced in the medial lemniscus and postcentral gyrus following anesthesia (84), even though their latency was slightly prolonged (31) and the recovery time to paired shocks was extended (174).

The above evidence clearly indicates that anesthetics do not prevent impulses conducted in primary systems from reaching the brain, even though such cortical inputs arrive in a somewhat modified form. In the case of more widely distributed cerebral potentials, a paradox exists. Responses with moderately long latencies (12 to 30 msec.) evoked in widespread cortical loci from sensory nerve or reticular formation stimulation are obtainable only in the unanesthetized preparation (198, 262) while the 'secondary' response of Forbes (77), also conducted presumably through centrally located pathways in the brain stem, is enhanced by barbital anesthesia. The answer may lie in Morison's suggestion (Morison, R. S., personal communication) that the latter projections traverse an extrathalamic route while the former are conducted by thalamic as well as by subthalamic structures.

The effects of anesthetic agents upon spontaneous and driven cortical EEG rhythms are well established, but interpretation of the mechanisms involved has varied considerably. In general, cortical desynchrony and alpha rhythms which accompany wakefulness are replaced by the synchrony and spindling of sleep following anesthetic administration. Moreover, rapidly repetitive stimulation (e.g. 50 per sec.) of the reticular formation, either directly or through excitation of its collateral sensory input, does not result in activation of the record in the anesthetized animal (12, 80). In contrast, the recruiting response elicited by 6 to 12 cps stimulation of the diffusely projecting thalamic nuclei is enhanced by barbiturates, although ether blocks this response as it does EEG activation (140).

In addition to elimination of the arousal response, anesthetic agents seriously modify caudally-directed functions of the RAS which are expressed upon motor and sensory systems. Blockade of brain-stem activity, such as is known to exist in the anesthetic state, renders the subject quite atonic and incapable of voluntary or even reflex movement. Animals which were made chronically spastic by extirpation of the cruciate region relaxed under anesthesia (205), suggesting that tonic facilitatory influences from the reticular formation ceased with anesthesia.

However, there are divergent effects of drugs upon the reticular formation which make it necessary to re-examine the thesis that desynchrony is the inevitable electrographic behavioral manifestation of wakefulness and that synchrony and sleep always occur together. Funderburk & Case (87) have shown that atropinized animals appear awake and alert yet exhibit a synchronized EEG and the observation has been confirmed by Bradley & Elkes (30). It might be proposed that atropine blocks a cholinergic desynchronizing mechanism in the reticular formation (236) yet does not interfere with other reticular phenomena related to the preservation of behavioral wakefulness. By contrast, reserpine tends to induce inattentiveness and drowsiness without synchronizing the low voltage fast activity in the EEG (139). Mephenesin, an interneuron blocking agent without anesthetic properties, depresses the recruiting response elicited by stimulation of the diffuse thalamic projection system but does not alter EEG arousal from the mesencephalic reticular formation (140). Chlorpromazine causes only a slight increase in stimulus threshold for EEG arousal from thalamic stimulation but increases by 10-fold the current required to elicit behavioral arousal from the same site (139). Behavioral and EEG arousal following reticular formation stimulation were not critically affected by this drug.

MOOD-ALTERING DRUGS. The evidence available at present concerning the mode of action of the so-called 'mood-altering' drugs is not only meager but highly confusing as well. Leake (147, 148) and others have called attention to the fact that all substances which induce these changes in 'mood' have in common an indole or indole-like linkage in their chemical structure. It has been further pointed out (147) that epinephrine and in particular its metabolites, such as adrenochrome and 5-hydroxytrytamine (serotonin), contain this linkage. Moreover, other substances such as lysergic acid-diethylamide (LSD) and even the alkaloids, cocaine, atropine and morphine have important structural similarities. All of

these agents when administered to man in appropriate doses have the common property of altering perceptive experience.

It is possible that the 'psychogenic' properties of drugs such as LSD relate in general to actions which tend to excite reticular function just as do such stimulant substances as epinephrine, acetylcholine, and 5-hydroxytrytamine. Amphetamine and other excitatory drugs are known to exert a facilitating effect upon the reticular formation (12, 60). LSD, a compound somewhat similar in structure and effect to 5-hydroxytrytamine induces symptoms characterizing psychotic behavior rather than sleeplessness. Yet LSD desynchronizes the EEG as do other excitants such as amphetamine (29). Leake (147) suggests that the direct effect of epinephrine upon the brain is depressant, and Marrazzi (173) has demonstrated that it is a powerful synaptic inhibitor when injected into the cerebral circulation. Leake feels that its excitant action upon central nervous structures stems from its peripheral action and is secondary to proprioceptive feedbacks into the brain stem.

It was proposed initially that chlorpromazine and reserpine exerted an anesthetic-like effect upon reticular function (116, 117). Recent evidence, however, indicates that EEG activation to reticular formation stimulation is only slightly altered by these drugs (28, 138), although behavioral arousal from excitation of the thalamic portion of the reticular system is somewhat more depressed. The relative inattentiveness displayed by animals given chlorpromazine may relate principally to its action upon sensory modulating functions of the reticular formation to be described later (11, 138). The increased reticular inputs which are known to attend chlorpromazine administration are thought to enhance caudally-directed inhibitory influences exerted upon afferent conduction (138). This inhibition, coupled with a depressed cephalic influence exerted upon cerebral structures (arousal response), would appear to contribute importantly to 'tranquility.'

The fact that Parkinson-like tremor may be manifested following excess chlorpromazine and reserpine ingestion suggests that an action upon the reticular formation may relate to this toxic symptom. Tremor is known to arise when lesions are made (227) or when stimulation is applied (284) to the central brain stem. Drugs such as scopolamine may inhibit tremor by diminishing the cholinergic excitability of the reticular formation.

DESCENDING INFLUENCES

It is probable that all motor activity is accomplished through modulation of segmental reflex patterns by inter- and suprasegmental influences (71). Discharges are elicited in the motoneuron, the instrument of the final common path, in response to local sensory driving, but the primitive purposes subserved by pure reflex activity have required amendment to permit the addition of postural modification and volitional direction to this local phenomenon. Implicit in the process of encephalization is the requirement that a major portion of these calibrating and driving influences emanate from the cephalic or direction end of the modified neuraxis. It is now known that the brain mechanisms concerned with postural regulation exert their influences in large part through the reticular formation. (See Chapter XLI of the *Handbook* in which Eldred discusses postural mechanisms.)

Orthodox concepts concerning the influences of the brain upon tonic muscle function stemmed from the observation that an animal is rendered spastic by a transection of its neuraxis in the midbrain and remains so as more caudally located transections are successively made until the region of the vestibular nuclei is reached. Division of the brain stem just below this level results in the disappearance of spasticity, and following the explanation by Magnus, it was held that the enhancement of tone observed in the decerebrate preparation was maintained by vestibulospinal activity. In 1932, Allen (8) offered an alternative suggestion. "On the other hand, it might be explained that the section below Deiters nucleus eliminated all or practically all of the connections of the formatio reticularis of the brain stem." In 1946, documentation of this proposal began to be provided by Magoun and his associates who found that the reticular formation was capable of exerting pronounced facilitation and inhibition upon spinal motor activity.

Inhibition

Magoun & Rhines (171, 172) described experiments upon decerebrated or anesthetized cats in which movements induced by evoking reflexes or exciting the motor cortex were immediately inhibited or abolished when the reticular formation was stimulated. Clearly this inhibition was transmitted by rapidly conducting neurons as its effect reached a maximum after 9 msec. (15). Furthermore, it could be evoked by brief low-threshold shocks of wide frequency range. The descending reticulospinal fibers involved are

diffusely scattered throughout the anterior and lateral funiculi of the spinal cord (205) and, while the most prominent inhibition was observed ipsilaterally, bilateral effects were easily demonstrated.

The brain-stem area from which inhibition could be induced was originally thought to be confined to the medioventral reticular formation at the bulbar level (205). Subsequent observations by Hodes *et al.* (119), however, described effective loci throughout the cephalic neuraxis to and including the septal nuclei. Austin (15) likewise was able to elicit inhibition by stimulation of points in the region of the posterior commissure, center median nucleus of the thalamus, stria terminatis and red nucleus. The inhibitory effects first described were general and nonreciprocal (171, 172, 261), but Bach (16) was able to record reciprocal responses. Later, Sprague (258, 260) found that reciprocal effects were induced by stimulation of some points within the reticular formation, and nonreciprocal responses from others. Gernandt & Thulin (97) confirmed these effects of reticular stimulation by demonstrating both reciprocal and nonreciprocal inhibition of ventral root reflex responses. The two-neuron stretch reflex was found to be particularly susceptible to the inhibitory influences of the reticular formation while, concurrently, the polysynaptic reflex was commonly, although not uniformly, found to be facilitated (15, 97, 144).

The existence of interneurons in the spinal cord which have exclusively inhibitory properties was originally proposed by Renshaw (225) and more recently expanded by Eccles *et al.* (70). It is convenient to think that specialized cells of this kind may relate closely to the mediation of suprasegmental inhibitory influences, but as yet no definitive evidence confirming this possibility is available. Support for the concept, however, is supplied by Lettvin who found that fibers from an inhibitory reticular area end in the lateral portion of the internuncial pool (150) and that direct stimulation of this spinal region with microelectrodes suppressed motor neuron activity.

Facilitation

In contrast to the inhibitory effects elicited by stimulation of the medullary reticular formation, Magoun & Rhines found that facilitation of spinal motor activity could be initiated by comparable stimulation of loci higher in the central brain stem. These effects were induced by excitation of the bulbar reticular formation, midbrain and pontile tegmentum, periaqueductal grey substance, sub- and hypothalamus, and from the mid-line, intralaminar nuclei and nucleus ventralis anterior of the thalamus. Peacock & Hodes (210) subsequently observed that facilitatory influences could be elicited from still more rostrally located sites, for example, from the septum.

As with inhibition, this effect (169, 172) was elicited by low threshold stimulation and could be evoked by a wide variety of stimulus frequencies. Its rapidly conducting spinal path (93, 169) was bilateral and diffuse, located in the ventral and lateral funiculi. In general, facilitatory fibers were found to occupy more dorsal and inhibitory fibers and more ventral locations in the spinal cord, and each could be sectioned differentially (205).

Both the two-neuron stretch reflex and the multisynaptic flexor response are subject to facilitatory influences from these suprasegmental areas, although effects upon the myotatic response predominate in flexor and extensor muscles alike (15, 144). Facilitation of this response was accompanied either by inhibition or enhancement of the polysynaptic reflex (15, 144), although inhibition predominated (144). Both reciprocal (99, 260) and non-reciprocal (101, 266) effects have been observed.

The effects of brain-stem stimulation upon reflex activity in the spinal cord were found to be rapidly conducted (93), although, as with pyramidal excitation (44), recruiting build-up appeared to play an important role in the elicited response. Lloyd (163) showed that augmentation of the monosynaptic reflex did not occur immediately upon arrival at the spinal level of facilitating influences. The effect required much longer to become maximal and, as was found when studying inhibition, prolonged (15) or recurrent (144) facilitation was evidenced for as long as 10 sec. (15) following cessation of the brain stimulus. A rebound reversal effect also has been noted at the termination of a facilitatory stimulus applied to the reticular formation (97, 258).

In addition to augmentation of reflexly- or cortically-induced movements, facilitatory influences arising from stimulation of the brain stem can be made sufficiently great to evoke postural changes. Sprague & Chambers (260) reported that threshold bulbar stimulation near the mid-line initiated ipsilateral flexion and contralateral extension, while excitation of more laterally located points elicited the opposite effect. Such changes are related doubtless to the contrasting effect upon reflex activity elicited by medial and lateral loci in the RAS (97). Reticular formation excitation, therefore, particularly with

supramaximal stimulation, can augment the excitatory state of spinal neuron pools already subject to tonic reflex inputs to a degree which is sufficient to elicit movement (163, 258).

Suprasegmental Influences upon Segmental Motor Neuron Activity

Like pyramidal (44, 146, 164) and reflex systems, (except the myotatic reflex) the reticular formation appears to exert its facilitatory and inhibitory spinal influences principally through interneurons rather than upon motor neurons directly (163). Sustained reticular excitation recruits expanding pools of interneurons and these in turn summate their influences spatially upon motor neurons (163). Lloyd (165) suggests that faster reticulospinal influences may set the stage for impulses arriving over the more slowly-conducting pyramidal tract, and clearly both of these excitations sum together with local tonic inputs to elicit appropriate motor neuron excitation. Reticular influences appear to be more enduring than are those conducted via the pyramidal tract. Kleyntjens *et al.* (144) found that facilitatory effects elicited by pyramidal activation lasted only for the duration of the stimulus, while reticular excitation elicited prolonged facilitation which outlasted the stimulus by many seconds (15, 144).

The excitatory state of the anterior horn cell is modified by changes in depolarization induced 'synaptically' in it (69) and, presumably, reticular formation excitation elicits spinal facilitation or inhibition by initiating such potential shifts. Local catelectrotonus induced experimentally in the spinal cord was found to augment motor neuron firing (21, 36) while anelectrotonus appears to inhibit segmental motor activity (151, 266, 267). Comparable results were seen to follow stimulation applied to the reticular formation (94).

The reticular formation is now known to exert powerful controls over sensory receptor and conductor systems. This phenomenon will be discussed in more detail later but must be mentioned here in connection with motor systems, as gamma efferent neurons which control activity of muscle spindles are subject to reticulospinal influences (71, 101, 102). Through this mechanism, so far found to be predominately inhibitory in nature, suprasegmental structures exert powerful controls over reflex activity by modifying spindle discharge rates.

Reticulopetal Inputs to Reticular Formation

Whether or not the reticular formation is capable of independent tonic activity, certainly afferent inputs from the cerebral cortex, cerebellum, basal ganglia, vestibular nuclei and sensory transmission systems to the central brain stem influence it critically in the performance of its contributions to muscular control.

CEREBRAL CORTEX. All active cortical loci, along with their multiplicity of other functions including arousal, are known to exert an important measure of control over voluntary and reflex somatic motor function. Stimulation of some of these regions excites motor movements; classically, such activity is known to arise from activation of the motor and premotor cortex as well as from frontal and paraoccipital eye fields. Contrastingly, excitation of other cortical loci appears to inhibit rather than initiate motor movement. Hines (118) first reported inhibition of existing muscular contraction by stimulating area 4S (between areas 4 and 6) and subsequently Dusser de Barenne and associates (66, 68) designated four other zones as 'suppressor' strips; these loci were situated in the frontal and parietooccipital eye fields, postcentral gyrus and cingulate gyrus. All of these cortical loci, stimulation of which either initiates or inhibits movement, are known to have intimate anatomic and physiologic relationships with the reticular formation and to exert a considerable measure of control over its activities.

A principal reason for considering these loci as 'suppressor' strips was that their excitation was thought to express an inhibitory action upon the myotatic reflex by way of the reticular formation (177). In support of this concept was the observation that resection of area 4S resulted in transitory spasticity, presumably because this loss of suppressor input to the reticular formation permitted unbalanced facilitatory influence from the brain stem or vestibule to augment myotatic activity in the spinal cord (156, 160). Also, Sloan & Jasper (250) showed that arrested activity similar to that induced by stimulation of thalamic portion of the reticular system (121) is elicited in unanesthetized animals by stimulation of the cingulate gyrus. Comparable cessation of movement has been noted by Segundo *et al.* (244), by Kaada (131) and by Clark *et al.* (55) following stimulation of the active cortical loci—'suppressor' as well as movement-inducing. Clark *et al.* (55) correctly indicated, however, that tone was not eliminated by cingulate stimulation in the dog; the animal ceased to move but did not collapse, and suppression of

movement induced by stimulation of the motor cortex did not occur until the animal was anesthetized.

Both facilitatory and inhibitory influences appear to be expressed from active cortical loci; it is even likely that excitation and suppression both can emanate from the same locus under different conditions. von Baumgarten *et al.* (270), for example, reported that single shocks applied to the motor cortex were followed at times by augmentation and at other times by inhibition of responses in a single unit in the reticular formation, depending doubtless upon the local state of both stimulating and receiving cells. In this regard, Livingston & Fulton (161) have called attention to the fact that effects of cortical excitation vary considerably according to stimulus characteristics and temporal levels of excitability. Eliasson was able to elicit both excitatory and inhibitory responses in gastric motility upon stimulation of the cingulate gyrus (72). In the unanesthetized alert animal, Segundo *et al.* (244) found that a state of immobility was initiated by stimulation of modulating cortical zones with threshold voltages while excessive activity followed supraliminal stimuli.

Considerable question has been raised concerning the validity of considering the active cortical loci enumerated as 'suppressor' zones (189, 190, 249). While it is probable that many of these objections are valid, it seems clear that loci to which the term 'suppressor' was originally assigned contribute importantly to modulation of motor mechanisms as well as to other caudally and cephalically directed influences mediated by the reticular formation.

It has been proposed that part, at least, of the cortically-originating influence over motor functions requires cortical re-entry after brain-stem transport in order to exert its control by way of pyramidal or extrapyramidal routes (46, 119, 210). Moreover, it has been suggested that facilitation of motor cortical response by brain-stem stimulation occurs within the motor cortex itself (200). Supporting this concept are the observations that motor abnormalities, such as tremor, are improved by destruction of re-entrant channels to the cortex from basal ganglia (57, 188) and from the cerebellum (108). Yet movements elicited from stimulating the pyramidal tract after extirpation of the cortex are still facilitated by brain-stem excitation (169). Reticulospinal influences appear to exhibit some measure of independence from the cortex, therefore, although there can be no doubt that properly functioning cortical structures are necessary for normal control of tonic and phasic muscular activity.

CEREBELLUM. In 1896 Sherrington (246) showed that faradization of the anterior lobe of the cerebellum inhibited the extensor rigidity of animals with all structures above the mesencephalon destroyed. Later, Bremer (32) confirmed this observation and noted in addition that excision of the cortex in this region resulted in a strong increase in decerebrate rigidity. Evidence is abundant now which indicates that such cerebellar influences as these over motor functions are mediated principally through reticulospinal connections (196, 253).

It is now evident that both facilitatory and inhibitory influences can be elicited by stimulation of the cerebellum (252, 254, 255). In fact Moruzzi suggests that the nature of the influence induced is a function of cerebellar discharge rate and that "every Purkinje cell of the anterior vermis may be inhibitory or facilitating according to the frequency of its discharges" (195). Both facilitatory and inhibitory responses can be elicited by excitation of the same cerebellar site with different stimulus frequencies. Nulsen *et al.* (206) suggested that anterior vermal stimulation at faster pulse rates elicited facilitatory influences, while Snider *et al.* (255) found reverse relationships. Doubtless a species difference is important as the cat and monkey reacted differently.

The most recent proposal concerning the functional relationship between cerebellum and reticular formation is that of Chambers & Sprague (51). They suggest that this relationship is oriented longitudinally in both structures. The medial cerebellar zone consists of the vermal cortex which acts through the fastigial nucleus upon the central reticular formation and is concerned with postural tonus equilibrium and locomotion of the entire body. The intermediate zone arises in the paravermal cortex and acts upon the lateral reticular formation via the nucleus interpositus and superior peduncle. This zone is considered to function in more discrete control of the use of ipsilateral limbs.

A feature of the cerebellar-reticular interrelationship which bears comment is the apparent functional organization which is displayed by stimulus sites in the cerebellar cortex. Nulsen *et al.* (206) showed that a high degree of specificity could be demonstrated by cerebellar stimulation; discrete activation of specific folia only would augment or inhibit single muscles thrown into movement by cortical stimulation. The organization of the motor proprioceptive homunculus on the cerebellum seemed to coincide quite closely with the sensory homunculus described by Snider and Stowell (252, 256). By contrast, no such organization

pattern has been described for the reticular formation. That some such order may exist, however, is indicated by the microelectrode studies of Scheibel *et al.* (241) and Hernández-Peón & Hagbarth (111) who were able to activate some specific units in the reticular formation by cerebellar polarization, but not others. This matter clearly requires additional attention. (The reader may care to consult Chapter LI in this *Handbook* which considers cerebellar function.)

VESTIBULAR SYSTEM. Following early truncation experiments it was suggested that vestibular function was facilitatory in nature and that its powers were exerted directly upon the spinal cord (168). Subsequently, it was demonstrated that, while decerebrate rigidity is ameliorated by vestibular destruction (18, 156), facilitation of cortically- or reflexly-induced movement could be elicited by brain-stem stimulation after destroying vestibular nuclei or interrupting their descending connections (18). It was concluded, therefore, that both structures (reticular formation and vestibular nuclei) acted upon segmental reflexes.

It has been suggested that vestibular influence is directed principally at control of tonic reflex activity while the reticular formation is concerned chiefly, if not exclusively, with phasic responses (18). Because of the functional relationships between brain-stem structures, however, it is doubtful that a clear distinction of this kind can be supported. Ample evidence now indicates that vestibular influences upon somatic motor mechanisms are inextricably associated with those of the reticular formation (95, 96, 135, 167), and such connections are now known to represent the principle route through which vestibular influences are exerted upon the spinal cord (96). Thus, while the vestibular nuclei are capable of acting directly upon spinal reflexes, much more potent vestibulospinal influences are exerted by way of the reticular formation.

Vestibuloreticulospinal influences are bilateral, and reciprocal effects upon flexor and extensor muscles have been reported (96). In addition to being reciprocal, however, responses appear also to be reversible as discharges from a single reticular cell were augmented when the head was turned in one direction (vestibular stimulation) and suppressed when turned to the opposite side (95). Reticulospinal excitation was found to be tonically energized by the vestibular apparatus as bilateral eighth nerve section caused the monosynaptic reflex to diminish and its latency to lengthen (96). Vestibulospinal conduction was very rapid; the direct response had a latency of 4 to 5 msec. to the ventral root of L7 while vestibuloreticulospinal transport required 7 to 9 msec. (93).

BASAL GANGLIA. It is well known that the basal ganglia form an integral part of the 'extrapyramidal' system, yet no striopallidal effector pathway directly to the spinal cord has been demonstrated. It has been proposed that the principal influence of basal ganglia upon spinal motor activity is exerted through thalamic and cerebellothalamic reverberation to the cortex and through pyramidal or parapyramidal transport (47, 86). While such reverberation doubtless has functional importance, it is also probable that activity generated within the basal ganglia is expressed directly upon the spinal cord by way of the reticular system (55, 170). The striatum is known to relate anatomically with activating cortical zones (98) and with the reticular system (65, 223). Striopallidal contact with the cortex (68, 176) and with the thalamic and brain-stem reticular system (247) has been established by physiological testing. Pathways exist, therefore, to mediate direct as well as cortical transmitted influences from basal ganglia.

It has been reported that stimulation of the striatum does not elicit movement, hence that the basal ganglia required a background of cortically induced movement to operate (86) Supporting this concept are the observations that movements or postures elicited by cortical excitation are inhibited (86, 186) or are transferred into a state of plastic tonus (185) by pallidal stimulation. Contrastingly, Sweet *et al.* (264) have demonstrated that excitation of pallidal outflow in preparations in which the cerebral peduncles had been transected resulted in repetitive movements of the extremities. Ward (284) was unable to elicit inhibitory responses upon stimulating the caudate nucleus of unanesthetized animals.

That the basal ganglia exert an inhibitory influence upon motor mechanisms which is not conducted via the pyramidal tract is suggested by the fact that spasticity is elicited by cortical motor resection and that it is enhanced by subsequent striopallidal destruction (160, 184, 243). Conflicting evidence is supplied by clinical observations in which tremor and spasticity are alleviated by surgical lesions made in the basal ganglia (57, 188, 257) thereby, according to Cooper (57), eliminating facilitatory contributions to muscular tonus and movement.

In view of conflicting evidence, therefore, it must be supposed that the basal ganglia contribute to motor mechanisms largely by virtue of their connections with the thalamic and brain-stem reticular sys-

tem. Additionally, however, striopallidal influences must be strongly energized by cortical inputs and are probably expressed through cortical re-entrant circuits. It is difficult, if not impossible, to label these pallidal contributions exclusively facilitatory (57, 170) or inhibitory (47, 86, 158) and, as has been described in connection with other structures (e.g. cortex, cerebellum, etc.), probably elements of each are to be discerned. In view of rekindling of clinical interest in the matter, however, it is painfully clear that striopallidal mechanisms require considerable reassessment.

SENSORY INPUTS. As excitation of peripheral nerves or sensory pathways in the central nervous system is known to activate cephalically-oriented influences mediated by the reticular formation (e.g. the arousal response), it might be supposed that afferent excitation elicited in the brain stem would also energize caudally-directed activities such as those exerted upon muscle function and sensory conduction. Affirmative evidence is extensive which indicates that reticulospinal energies are influenced by sensory inputs, hence only a few illustrative examples will be cited. Abbie & Adey (1) showed that the frog with cerebral and cerebellar structures removed was still able to maintain a good posture, presumably through retained function of its brain stem. When dorsal roots were divided, however, the postural response was eliminated. von Euler & Söderberg (273) were able to show that, while cells in the brain stem normally exhibit a background of activity, the deafferented medulla was relatively silent when tested for unit firing.

It has been demonstrated also that bulbospinal discharges can be driven by sensory stimulation (270). On the other hand, removal of sensory inputs is known to deplete spinally-directed influences from the reticular formation as division of the vestibular nerves resulted in increased latency and diminished amplitude of the monosynaptic response (96).

Spasticity

It is probable that all motor functions—not only maintenance of normal tone but also mediation of conditioned responses and voluntary motor movement—can be explained on the basis of segmental reflex activity as modified locally by inter- and suprasegmental influences. Eldred *et al.* (71), following a study of brain-stem control over gamma efferent neuron activity and thus of the muscle spindle, concluded, "Rough measurements . . . indicate that the range of bias at the command of supraspinal centers is adequate to cover the whole physiological range of movement." Hence, it is necessary to consider that the flexibility necessary to perform all degrees and kinds of muscle activity resides in each segment of the spinal cord. Skilled and voluntary actions are initiated when the responsiveness of these local mechanisms is changed and this change is elicited by highly integrated facilitatory and inhibitory influences arising in cerebral structures.

It is probably inappropriate to attempt a division of suprasegmental influences into separate systems which concern primarily tonic or postural phenomena and those which modify phasic activity. There is no doubt now that brain-stem stimulation can elicit both nonreciprocal and reciprocal neuromuscular responses. The former clearly subserves not only tone and posture but also the stabilization of joints by nonreciprocal contraction of muscles during voluntary motor activity (93). The latter permits positioning of the trunk or limbs in keeping with the requirements of voluntary movement. Implicit in reciprocal responses is the fact that the myotatic reflex of the agonist must be facilitated at the same time that the myotatic reflex of the antagonist is inhibited. It is true that some division exists in the brain stem between stimulus sites which elicit nonreciprocal responses and those which induce reciprocal patterns, yet this parcellation is by no means mutually exclusive. Further, inputs to these respective brain-stem zones in general can no longer be classified specifically as 'tonic' or 'phasic' contributors. For example, the vestibule connects with both enhancing and suppressing portions of the reticular formation and activity elicited within the labyrinth induces change in tone as well as position (97).

While anatomical division of the brain stem into 'facilitatory' and 'inhibitory' zones is difficult, clearly such a division exists functionally. Also these brain-stem 'centers,' while exhibiting some sustained or automatic activity of their own (60, 155) are controlled by inputs from the spinal cord, cerebellum, cortex, vestibule and basal ganglia. In general, each of these inputs appears capable of supplying either facilitatory or inhibitory energies; doubtless one of the two predominates normally in all systems, although the determining or governing features remain obscure.

It is difficult, and possibly unnecessary, to tamper extensively with classical concepts of decerebration. Extensor rigidity increases as brain-stem transection approaches the level of the vestibular nuclei and dis-

appears following division below this region. It is convenient to consider in explanation that the successive transections eliminate inputs to the reticular formation which are more inhibitory than facilitatory thereby creating an imbalance in reticulospinal output in the direction of facilitation. With each successive additional transection, less and less suprasegmental control over reciprocal function, tonic or phasic, is retained. Finally, the last transection eliminates most, if not all, that is facilitatory, leaving only inhibitory centers or none at all.

As in truncation experiments, alterations of the tonic state can be achieved by surgically modifying the cerebral loci which appear to be particularly concerned with motor systems. In cats, transient spasticity can be induced by local resections of the pericruciate region (156, 184, 243), the cerebellar vermis (32, 156, 158) and striatum (156, 184) and destruction of all three increases and prolongs the rigidity. This effect is subject to marked phylogenetic variation, as in the frog, for example, fairly normal appearing postures are possible in animals with the bulk of the brain removed (1). In contrast, primates exhibit severe postural rigidity and phasic incapacity from cortical motor resection alone. (Clinical spasticity is discussed also by Denny-Brown in Chapter XXXII of this *Handbook.*)

PARAPLEGIA. The data support in general the concept of brain-stem facilitatory input to segmental reflex structures rather than of spinal release in explanation of decerebrate rigidity (156, 169, 172). The problem of clinical spasticity, however, presents additional considerations. Paraplegic transections below the brain stem, principally in the lower cervical and upper thoracic regions, initiate flaccid paralysis due, presumably, to elimination of suprasegmental influences and to spinal shock. As time elapses, however, spasticity develops and may progress to heroic proportions. Both hypertonus, commonly in flexion, and hyperreflexia are displayed. As suprasegmental inputs to the spinal cord are impossible as an explanation of these states, other causative agents must be sought.

A contributing feature to the spasticity of chronic paraplegia may be the 'artificial synapse.' Granit *et al.* (103) have demonstrated that impulses are 'short-circuited' in acutely injured or transected peripheral nerve; the excitatory discharge normally conducted in a single fiber 'leaks' into others. In the spinal cord it would appear that such diffusion of excitation could lead to mass-discharge. Renshaw & Therman (226) showed that a similar phenomenon can and does occur following incision within the spinal cord and the observations of Scarff & Pool (237) suggest that in human paraplegics short circuiting is a prominent feature at the proximal end of the distal segment below a transection.

Another factor in the production of the spasticity of paraplegia may be related to ephaptic discharge. It has been suggested repeatedly that, in contrast to synaptic transmission, one cell in the nervous system may be capable of influencing its neighbor extrasynaptically (or ephaptically) simply by virtue of proximity (14, 35, 91). Transection, conceivably, could enhance or initiate such discharges in the spinal cord.

Finally, influences characterized by the Schiff-Sherrington phenomenon possibly participate in the spastic state of paraplegia. It can be demonstrated that an increase in decerebrate rigidity can be induced in thoracic neuromuscular segments following transection at the thoracolumbar level (94, 233). This transection presumably eliminates tonic inhibitory influences arising in the lumbosacral region from the upper spinal cord. These observations imply that inhibition and perhaps facilitation can arise in the spinal cord itself. Transections inducing paraplegia doubtless severely distort these influences.

AKINETIC MUTISM. In 1941 Cairns *et al.* (48) described a patient with a cyst of the third ventricle which pressed intermittently upon the mesencephalic brain stem, inducing a state of immobility and vocal silence called akinetic mutism. Ingraham *et al.* (122), Bailey & Davis (19) and others (Ross-Duggan, J. & K. Richland, unpublished observations; Skultety, F. M., personal communication) were able to produce a somewhat similar syndrome in cats, and Peterson *et al.* (211) and others (81) in monkeys by placing lesions in the region of the caudal hypothalamus-midbrain tegmentum and the periaqueductal gray substance.

In his analysis of the problem, Magoun (169) suggested that lesions responsible for this condition of hypokinesis interfered with reticular influences directed cephalically as well as caudally. There appears to be, in milder degrees of akinetic mutism, an element of lack of 'will' or of conation similar to that exhibited by certain patients with lesions of the cingulate gyrus (203), suggesting that cerebrothalamic processes may have been rendered deficient by the lesion. This defect coupled with deficiencies induced in brain-stem facilitatory mechanisms were thought to be responsible for the described syndrome.

Tremor

In 1950 Magoun (169) reviewed existing information concerning mechanisms active in the experimental production of an alternating tremor of rest comparable to the tremor of parkinsonians. While additional information on the subject has become available since that time, the nature of the disorder underlying this rhythmically iterated movement is still far from clear.

The tremor occurs during resting tonus and disappears during the initial phases of activity and during sleep (169). Antagonistic muscles are reciprocally excited, creating the typical alternating movement at the rate of 6 to 10 cps. The tremor exhibits no constant rate, however, and frequency may differ in various localities where it appears. It does relate to muscle tension as increases in amplitude can be demonstrated in muscles subjected to passive stretch.

Tremor of this type has been induced experimentally by lesions placed in the ventral paramedian tegmentum at the level of the red nucleus in monkeys (211, 279, 282). When the lesion is unilateral, the tremor is displayed principally on the opposite side of the body (211, 279). A similar disturbance is sometimes seen following lesions placed in the region of the cerebellar nuclei (211) and superior cerebellar peduncle (50), although such tremors are prone to be complicated by accompanying dysynergia (211, 282). Yet Carrea (49) proposes that interference with portions of the brachium conjunctivum be considered the principal cause of these experimental tremors.

Ward & Jenkner (129, 281) have elicited a tremor, comparable to those induced by brain-stem lesions, in monkeys by stimulating rather than destroying the reticular formation. As this tremor is reduced by administration of cholinergic drugs, they suggest that tegmental lesions inducing tremor isolate cells in the reticular formation from higher structures; the tremor is due, then, to rhythmical facilitatory activity generated in these cells rendered hyperexcitable by sensitization of denervation (129).

Whether or not the above-mentioned concept is correct, many observations suggest that these induced disturbances have their origin in disordered reticular system function. It has been pointed out (282) that a supraspinal origin is clearly indicated by the persistence of tremor after posterior rhyzotomy (214) which eliminates the stretch reflex. It is possible that this suprasegmental influence can be conducted by way of the pyramidal tract, presumably because of abnormality induced in re-entrant circuits which traverse reticulocerebellothalamic structures (47). Credence must be given this possibility as it is well known that surgical lesions of the pyramidal system (47, 221) will stop the tremor as it paralyzes the involved musculature. Surgical lesions made in the nucleus ventralis lateralis of the thalamus, however, do not paralyze musculature but do eliminate the tremor in certain instances (108), whether by pyramidal or extrapyramidal conduction is not known.

Evidence suggests that rhythmic activity can be elicited in spinal motor pools through facilitatory reticulospinal pathways. Lloyd (163) showed that reticulospinal volleys have a pronounced synchronizing effect upon anterior horn cell discharge through propriospinal collaterals. Also, Gernandt & Thulin (97) showed that prolonged stimulation of the bulbar reticular formation resulted in a curious waxing and waning of the intensity of the monosynaptic reflex. Similarly, Kleyntjens *et al.* (144) reported the production of oscillations or fluctuations in reflex spike amplitude following stimulation of the reticular formation, related possibly to a recrudescence of augmentation which followed cessation of a short facilitating volley to the brain stem.

Such evidence suggests that imbalance within the reticular formation is capable of inducing abnormal brain-stem discharge of a facilitating nature. It is anatomically possible for this disturbance to issue toward the motor neuron both through pyramidal and through reticulospinal channels. Both systems, together with segmental reflex activity, sum their effects at the motor neuron to create the nidus for movement. Apparently, however, reticulospinal mechanisms alone, if distorted, can reproduce rhythmic excitatory states at segmental levels and such oscillations doubtless contribute to tremor.

There is no information to explain directly why the addition of surgical destructive lesions to the basal ganglia or its outflows induces improvement not only in the tremor but also in the spasticity of parkinsonism (57, 188, 257). That it does so should create a vigorous stimulus for amplified investigations into the problem. (See Chapter XXXV in this *Handbook* on extrapyramidal mechanisms.)

AUTONOMIC MECHANISMS MEDIATED BY RETICULAR FORMATION

While neural mechanisms implicated in the function of the autonomic nervous system will be discussed in detail elsewhere in this work, particularly by

Ingram in Chapter XXXVII, a review of the physiological characteristics of the reticular system would be incomplete without brief comment concerning its contributions to visceral phenomena. There is abundant evidence which indicates that visceral mechanisms, residing in the brain stem, are subject to inhibitory and facilitatory influences from the senses, higher neural structures and products of metabolism in a way comparable to, if not identical with, those exerted upon nonvisceral mechanisms. It is becoming increasingly clear, in fact, that modifications in somatic function induced by physiological or experimental stimuli never occur without appropriate adjustments in visceral response (64).

Interrelationships between somatic and visceral mechanisms are indicated by the fact that stimulation by a single electrode placed within the reticular formation can rarely, if ever, be accomplished without inducing a variety of effects (17). The basic reports of Pitts *et al.* (213) and of Pitts (212) described two discrete areas ventrally and dorsally located in the medullary reticular formation which when stimulated elicited inspiratory and expiratory responses, respectively, in the respiratory rhythm of cats. Similarly, Wang & Ranson (278) were able to elicit pressor responses by stimulating the lateral medullary reticular formation and depressor changes by moving the excitatory electrode to more ventromedial loci in the bulb. Later, Bach (17) was able to confirm in a general way the existence of discrete loci in the reticular formation which were capable of inducing, when stimulated, appropriate modification of respirations or of arterial pressure.

It is tempting to conclude that medullary centers for enhancing or suppressing visceral activity function much as do comparable, even partly coextensive, brain-stem loci which influence somatic movement, and such a proposal has been made (17, 120). Recent investigations, however, do not entirely support concepts which assign exclusively facilitatory or inhibitory properties to specific brain-stem loci. Bach (17), studying the effects of stimulation applied to the medullary reticular formation simultaneously upon respiration, arterial pressure and induced reflex activity, found that usually all three processes were modified by excitation of each stimulus point. Furthermore, responses were not parallel in all instances; in fact, he found that simultaneous facilitation occurred in reflex response, respiration and arterial pressure in only 9 per cent of the stimulation points tested.

While emphasis here has been placed upon respiratory and vasomotor responses to stimulation of the reticular formation, examples abound of influences this brain-stem region exerts upon other autonomic mechanisms. The observations of Hemingway *et al.* (110) clearly indicate that mechanisms contributing to regulation of temperature control course from the preoptic area through the brain-stem tegmentum and enter in the lateral funiculus of the spinal cord with other reticulospinal fibers to terminate upon segmental neurons. Inhibition of shivering can be elicited by repetitive stimulation of loci along the extent of this axis in the reticular formation. Furthermore, structures contributing to mechanisms mediating gastrointestinal function (73), vomiting (25), the galvanic skin reflex (276) and a variety of other autonomic functions, reside in the same extent of brain stem reticular formation.

Inputs to autonomic centers in the brain stem parallel in many ways similar connections with the reticular formation which are known to function in control of somatic structures. No attempt will be made here to review specific sensory inputs to brain-stem 'centers' regulating respiration, vasomotor control, gastrointestinal activity and other autonomic functions for which the appropriate chapters in this *Handbook* should be consulted. In addition to specific excitation mechanisms, however, brain-stem regions implicated in autonomic regulation are susceptible to nonspecific impulses converging upon them from most, if not all, cranial and segmental sensory systems. Through such contacts, reflex responses—marked alteration in respiration following application of a painful stimulus to the skin is an example—are made possible. Thus, contributions made by somatic afferent systems to brain-stem autonomic control are comparable in every way to identical inputs which modify reticular formation participation in such of its other diverse functions as arousal, somatomotor control and sensory modulation.

Inputs from the cortex to the reticular formation are known also to exert important influences over visceral mechanisms mediated by the brain stem. In a previous portion of this review, evidence was presented which served to connect functionally discrete cortical loci residing in the frontal oculomotor, sensorimotor, cingulate, orbital, temporal, paraoccipital and rhinal areas with the reticular formation. These loci, known to be capable of inducing arousal and influencing somatic motor movement, when stimulated also elicit facilitatory and inhibitory effects upon visceral function (11, 132, 133, 215). For example, essentially all the cortical areas listed above have been implicated in gastrointestinal function (82). Paral-

leling these effects upon the gastrointestinal tract of excitation of cortical effector zones are observations concerning facilitatory and inhibitory influences exerted upon arterial pressure (20, 215), peripheral vasomotor tone (74), respiration (20, 136), pupillary reactions (251), galvanic skin reflexes (276, 277) and, indeed, upon all phases of autonomic balance.

Paralleling the results of stimulation in the reticular formation, the application of a stimulus to a single cortical effector locus elicits responses in many different effector systems. Bailey & Sweet (20), for example, found that a stimulus applied to the orbital surface of cats and monkeys inhibited respiration, caused a rise in arterial pressure and inhibited tonus in the gastric musculature; comparable accounts have dealt with excitation of other cortical loci (11, 215). The polyphasic responses elicited by cortical stimulation, however, often appeared logically interrelated and patterned into a recognizable behavioral unit (244). Segundo *et al.* (244), stimulating the several cortical effector loci in unanesthetized chronically-prepared animals, observed patterned responses appropriate to naturally-occurring behavioral situations. Threshold voltages elicited arousal, arrest of motion and attentive alertness; supraliminal excitation to the same loci induced roughing of the fur, increase in respiration, facilitation of movement—in substance, behavior normally attributed to fear and flight.

These responses to cortical stimulation are expressed by way of the neural connections each effector locus is known to have with visceral 'centers' in the reticular system. Normally-developed autonomic controls in higher animals and in man doubtless require cortical transport through utilization of these connecting pathways.

The intimate relationship between functional components of visceral and somatic effector systems is effectively demonstrated in truncation experiments. As a result of the classical experiments of Sherrington, effects upon muscle tone and reflex activity of progressively lowering the brain-stem transection are well known. Transection at the collicular level causes the animals to exhibit mild extensor rigidity. At the same time, respiration is little effected, only the beginnings of periodic breathing being displayed (120). In addition, vasomotor control is largely retained, while temperature control through panting (23) is impaired and through shivering (110) lost. Midpontine transection renders the animal far more rigid and causes it to display (particularly when vagotomized) highly developed periodic or apneustic breathing (265). At this point, control of vasomotor tone and support of arterial pressure are impaired, and mechanisms for control of temperature regulation are lost. As the transection is lowered to midmedullary levels, spasticity is lost, respiration becomes 'eupneic' or ataxic, and maximum loss of suprasegmental influence over vasomotor tone and arterial pressure is achieved.

INFLUENCE OF RETICULAR FORMATION UPON SENSATION

A recent development of the first magnitude has concerned the influence of the reticular formation in modifying sensory inputs to the central nervous system. Ramón y Cajal (222) long ago remarked upon the existence of centrifugal fibers which appeared to terminate in relay nuclei of sensory pathways. Now, evidence exists which indicates that efferent fibers of this type exert control over most, if not all, afferent conduction systems from receptor to cortex. This control is the subject of Chapter XXXI by Livingston in this *Handbook*.

The first evidence that central systems, particularly the reticular formation, influence sensory input was submitted by Granit & Kaada (102) for proprioception. Leksell (149) had demonstrated that muscle spindles were under the control of anterior horn cells of small size called gamma efferents. Granit & Kaada (102) and others (71, 100, 101) were able to show that reticular stimulation resulted in modification of gamma efferent discharge and hence of spindle activity.

Subsequently, similar controls were discovered in other sensory systems. Loewenstein (166) showed that the sensitivity of tactile organs in frog skin could be modified by excitation of sympathetic nerves to the test region and that these receptors could even be made to fire spontaneously. King *et al.* (142, 143) recorded a potential in the trigeminal nerve which followed the primary response elicited by peripheral stimulation and which they were able to show coursed peripherally from its central nervous system origin. It was suggested that these efferent potentials were capable of modifying peripheral skin receptors and might relate to such clinical disorders as trigeminal neuralgia. Granit (99) observed both facilitation and inhibition of retinal ganglion cells following excitation of the midbrain tegmentum. Galambos (88) found that auditory clicks recorded in the cochlear nerve were inhibited by stimulation of the olivocochlear bundle. Kerr & Hagbarth (137) were able to inhibit olfactory bulb potentials by excitation of

rhinencephalic structures. While the reticular formation has not yet been implicated directly in connection with all these peripheral receptors, its participation in the process of receptor sensitivity has been so well established as to indicate that it contributes a measure of control to all such systems.

Similar influence, as so far investigated largely inhibitory in nature, is known to be exerted by the reticular formation upon spinal and brain-stem sensory relays. Hagbarth & Kerr (107) found that responses evoked by peripheral excitation were inhibited by reticular formation stimulation in the posterior column, both the dorsal root reflex and dorsal column relay being involved. Scherrer & Hernández-Peón (242) reported that similar stimulation inhibited conduction in the nucleus gracilis, and Hernández-Peón & Hagbarth (111) noted comparable suppression in the sensory nucleus of the fifth nerve. Even transmission in the ventroposterolateral nucleus of the thalamus was seen to be modified by King *et al.* (141) following reticular excitation.

There is reason to believe that reticular modulation of sensory conduction is exerted tonically, at least afferent responses in the spinal cord are enhanced following high spinal transection or anesthesia (107, 155) or by destroying the reticular formation (112). In spite of such tonic discharge, however, it is evident that reticulopetal inputs contribute additionally to sensory modulation.

Hagbarth & Kerr (107) were able to elicit inhibition of conduction in the spinal cord by excitation of the sensorimotor, parietal and cingulate cortex as well as from the anterior vermis of the cerebellum. This inhibition due to cortical excitation was comparable to that elicited by stimulation of the bulbar and mesencephalic reticular formation. Kerr & Hagbarth (137) induced olfactory bulb inhibition by rhinencephalic excitation. Granit *et al.* (101) reported that excision of the anterior lobe of the cerebellum resulted in paralysis of gamma efferent mechanisms. Adey *et al.* (3) found that conduction within the reticular formation could be facilitated or inhibited by stimulation of all activating cortical loci including the rhinencephalon. Thus, as in other functions mediated by the reticular formation, that involved with control of sensory inputs is subject to modification from higher structures.

The implications and significance of these physiological observations is being explored currently and extensively by observations made on chronically prepared or conditioned animals. These observations are discussed elsewhere, and brief comment is made here only to suggest that assessment of the role served by the reticular formation in these studies will be of the utmost importance. Green & Arduini (105) were among the early observers to implicate the reticular formation in the phenomenon that animals adapt to repeated stimuli and are aroused most effectively by new and strange stimuli. Subsequently, great interest has been expressed in the electrophysiological correlates of habituation to monotonously repeated stimuli (89, 111, 112, 113) and conditioning (89, 113, 130). Already it has been possible to observe inhibition of photically-evoked potentials in the visual system during alerting elicited by acoustic or olfactory stimuli and stimulation of the reticular formation (114).

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Unspecific thalamocortical relations

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CHAPTER CONTENTS

INTRODUCTION

THE UNSPECIFIC THALAMOCORTICAL projection system constitutes the rostral portion of the ascending reticular activating system of the brain stem (54, 55). It is sometimes called the thalamic reticular system (39). It partakes of some of the properties of the more caudal portions of the reticular system in the basal diencephalon and midbrain with which it is closely connected. It serves to mediate and to distribute to almost all areas of cortex, some (although not all) of the ascending activation originating in the more caudal portions of the brain-stem reticular system. In addition, the thalamic reticular system maintains a more direct control over the rhythmic electrical activity of the cortex and may serve also as an intrathalamic integrating system.

The anatomy and distinct physiological properties of the thalamic reticular system were first described by Morison & Dempsey in 1942 (22, 23, 57). By exploring the thalamus with a stimulating electrode while recording the electrical activity from local areas of the cortex in the cat, they were able to discover a separate projection system originating in the intralaminar system of thalamic nuclei. The longer latency, widespread 'diffuse' distribution and 'recruiting' character of the cortical response to repetitive stimulation of intralaminar nuclei served to distinguish this projection system from the local short latency responses to stimulation of specific thalamic nuclei with known local cortical connections. These observations led Morison & Dempsey to the important conclusion that "there exists between thalamus and cortex at least two systems, with very different physiological properties: a, the well known specific projection system with a more or less point-to-point arrangement; b, a secondary non-specific system with diffuse connections" (57, p. 292). It was postulated that recruiting responses were mediated by the unspecific cortical afferent fibers described by Lorente de Nó (50).

The importance of the ascending reticular activating system, brought to light by Magoun and coworkers, was not known at this time. However, Berger (7, 8), Adrian (1) and Rheinberger & Jasper (71) had observed that there was a general mechanism for the regulation of the electrical activity of the cerebral cortex as a whole. It was related to processes of attention, alerting, general excitement or sleep, interpreted as the maintenance of a general level of cortical excitatory state (37).

The unspecific thalamocortical projection system was next encountered by Jasper & Droogleever-Fortuyn (42) in their search for the mechanism controlling the bilaterally synchronous generalized wave and spike discharge of petit mal epilepsy. It was found that the rhythmical electrical activity of the cortex of both hemispheres could be controlled into a synchronized electrical beat by repetitive stimulation of only a few square millimeters of grey matter in the center of the thalamic reticular system. Under certain rather ill-defined conditions a 3 per sec. stimulus would

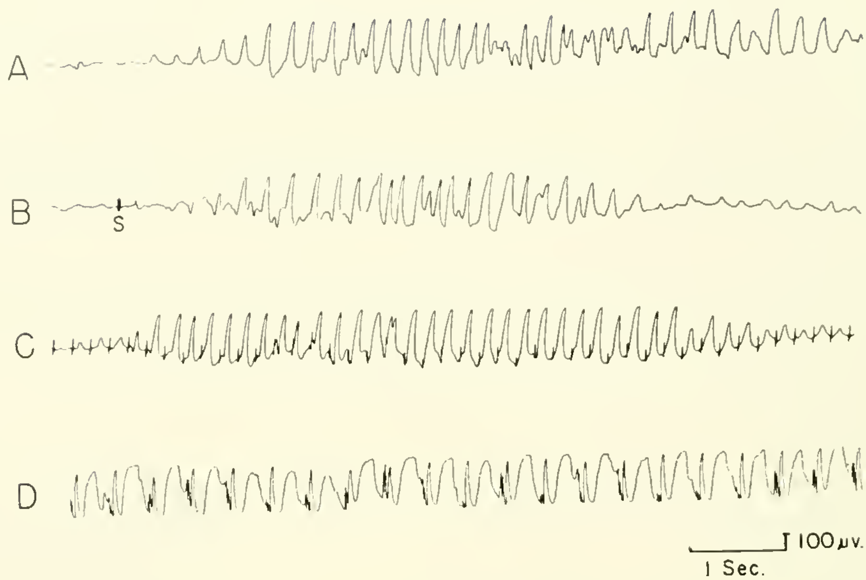

FIG. 1. Effect of unspecific thalamic stimulation in n. centralis medialis of the cat upon electrical activity from the anterior suprasylvian gyrus. The animal was under light pentobarbital anesthesia. *A:* Spontaneous spindle burst. *B:* A single 1 msec. shock (*s*) 'tripping' a spindle burst. *C:* Repetitive stimulation at 5 per sec. showing waxing and waning of recruiting response. *D:* Spike and wave response to stimulation at 2.5 per sec. (Unpublished records taken with J. Droogleever-Fortuyn.)

produce a regular wave-and-spike complex as seen in petit mal epilepsy (fig. 1*D*).

A topographical organization with respect to different areas of cortex was also demonstrated by carefully controlled local stimulation within different parts of the intralaminar system. Numerous electrophysiological and anatomical studies then followed to give a clearer picture of the structure and functional characteristics of the unspecific as compared to the specific thalamocortical projection system.

RECRUITING RESPONSE

A single electrical stimulus of brief duration administered to the central portion of the intralaminar system may result in little evidence of immediate response from the cortical surface. There occurs, however, a burst of rhythmic waves resembling the spontaneous (spindle bursts) of the resting cortex (fig. 1*A* and *B*). These bursts may begin in frontal or motor cortex after only a few milliseconds delay, but with delays up to several hundred milliseconds in more posterior areas of the cortex (fig. 2).

Repetitive stimulation at a frequency approximating that of the dominant spontaneous electrical rhythm (6 to 12 per sec.) results in the recruiting response (fig. 1*C*). Under optimal conditions this response is characterized by a successively increasing surface negative wave reaching a maximum after two to five successive stimuli. With continued repetitive stimulation the response may then progressively decline in amplitude and then recur again in a spindle formation, waxing and waning in a manner similar to spontaneous spindle bursts. During this time the recruiting response may completely dominate the cortical electrical activity, no spontaneous rhythms appearing. With strong stimulation, in a favorable preparation, responses may continue with little waning as long as the frequency of repetitive stimulation is kept within rather narrow limits.

Slower frequencies of stimulation may result in doubling of responses while frequencies above 12 per sec. may cause alternation of response. With higher frequencies, above 20 per sec., no responses may appear and the spontaneous rhythmic activity of the cortex may be completely arrested.

The latency of onset of the surface negative wave of the recruiting response is usually 20 to 40 msec. following the thalamic stimulus. However stimulation of the rostral portion of the system, in n. ventralis anterior and reticularis, may result in responses in frontal and motor cortex of shorter latency (5 to 10 msec.) and rapid recruitment, with a near maximum response even to the first of a series of stimuli. A recruiting response in the motor cortex with a latency of 10 msec. from stimulation of the rostral portion of the thalamus in n. ventralis anterior is compared with a response from the same cortical area conducted from a more caudal portion of the system in the centrum medianum is shown in figure 3. There is a shorter latency 'tripping' of spindle bursts and rapid

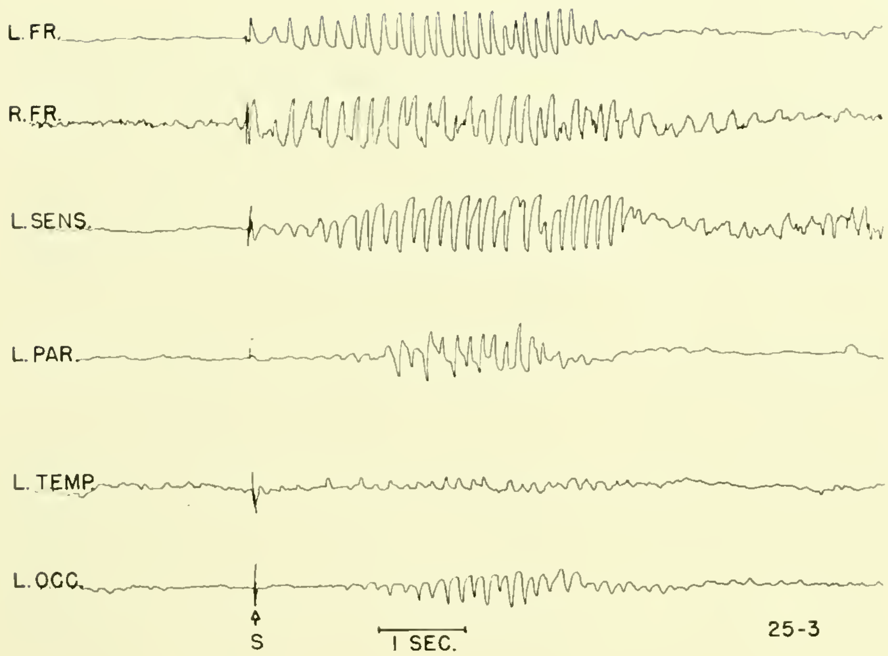

FIG. 2. Tripping of spindle bursts in six different cortical areas in response to a single shock in the intralaminar nucleus centralis medialis of the cat under pentobarbital anesthesia.

recruiting with less waxing and waning from rostral thalamic stimulation. Nevertheless responses show a wide distribution over many areas of cortex. Here one often obtains a mixture of specific and unspecific effects making analysis difficult.

The recruiting response is not always of surface negative electrical sign. When the surface of the cortex is depressed by exposure, or by the local application of procaine, the response may be entirely surface positive. It may also be diphasic with an earlier surface positive phase of smaller amplitude. Early positive phases may be due, however, to contamination by simultaneous stimulation of some specific projection fibers which produce short-latency initially surface-positive responses. There may be a typically surface-negative response in one cortical area simultaneous with a predominantly surface-positive wave in another area, the latter area usually being under less complete control by the recruiting system at a particular site of thalamic stimulation.

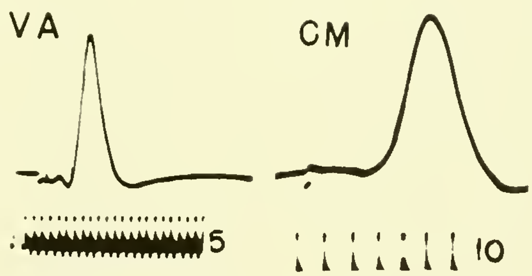

FIG. 3. Oscilloscope record of single waves of recruiting responses in the precruciate cortex of the cat, evoked by stimulation of n. ventralis anterior (*VA*) and n. centrum medianum (CM), respectively. Speed of sweep is indicated in 5 and 10 msec. time lines below.

MICROELECTRODE STUDIES OF RECRUITING RESPONSE

The intracortical distribution of unspecific afferent projections from the thalamus has been shown to be distinct from that of specific afferents by microelectrode studies (45, 46). The surface negative wave of the recruiting response becomes a deep positive wave when recorded with a microelectrode inserted to a depth of 0.7 to 1.0 mm beneath the surface. It represents, therefore, a wave of depolarization located in the more superficial cortical layers, comparable in this respect to the late surface negative wave of the specific evoked potential complex.

Individual neurons, which fire with short latency in the deeper layers of the cortex in response to a specific afferent volley, are not fired directly by impulses arriving over unspecific afferents. However, the excitability of these specific cortical cells can be modified so that they show increased firing to the

same specific volley if paired with an earlier unspecific conditioning volley.

Other individual cortical neurons can be fired by unspecific afferents after the recruiting wave has reached sufficient amplitude. These cells fire repetitively on the ascending limb of the recruiting wave and continue to fire during each wave until the waning phase of the response when they cease firing. Such units may fire with a delay of 20 to 30 msec. if the recruiting wave occurs with this latency.

The initial waves of the recruiting response always occur before unit firing, suggesting that the waves are primary, and serve to initiate neuronal firing; the waves do not result from neuronal discharge. This is shown more clearly in a deeply anesthetized animal; no unit firing can be found with microelectrodes at any depth in the cortex, yet the recruiting response appears sometimes of even greater amplitude. The recruiting waves are therefore considered analogous to 'synaptic' or 'dendritic' potential waves, not depending upon the firing of the larger cortical cells.[1]

There is a growing body of evidence in favor of the conception that recruiting waves of the cortex of the unspecific type fall into the class of responses or activity called 'dendritic' (9, 13, 14, 16, 17, 20, 67, 68, 83). This implies that they do not depend upon the actual all-or-none firing of cortical cells and is consistent with the variable relationship found between cell firing and these waves in microelectrode studies. Also they can be recorded when the firing of cells has been suppressed by anesthesia. 'Recruiting' implies the successive addition of increasing numbers of units to the response. If these waves represent summation of successive increments of depolarization upon a dendritic network which possesses a long time constant and no refractory period, the addition of an increasing number of units would not be necessary to explain the potential changes recorded, as pointed out by Clare & Bishop (18, 19). Furthermore, the frequency specificity of this response in close relationship with the spontaneous electrical rhythms indicates driving of an 'oscillating' or rhythmic system (84). The frequency of stimulation must approach the periodicity of the 'oscillating' system to be effective. It has been suggested that these are the properties of dendritic networks in central grey matter (9, 83). There remains the possibility that small interneurons of the Golgi II type may play a role in cortical activity which is classified as 'dendritic' (46).

Anatomical studies provide some evidence in favor of these conceptions. The description of unspecific afferent fibers to the cerebral cortex by Lorente de Nó (50) stimulated Morison & Dempsey to postulate the existence of the unspecific thalamocortical projection system, even though no connection had been shown between intralaminar nuclei of the thalamus and such afferent fibers in the cortex. Chang has suggested that dendritic responses are mediated by axodendritic synapses as contrasted with the axosomatic synapses which would presumably characterize most specific afferent terminals. Such a classification of synaptic terminals, suggested by Ramón y Cajal (70), may be of far reaching physiological significance due to the special properties of dendrites summarized by Bishop (9). It has yet to be shown, however, that the projection fibers to the cortex from the thalamic reticular system are actually of the unspecific axodendritic type. Evidence from the work of Nauta & Whitlock (62) would suggest that such terminals may originate in either specific or unspecific thalamic nuclei.

[1] The increasing amplitude of the recruiting wave has also been shown to cause an increased number of cortical cells to fire, but the principal effect appears to be on the number of repetitive discharges in a given cell. Certain other cells, which are firing spontaneously before a recruiting response, may become grouped so that they give rise to brief bursts by the recruiting waves, even though this may represent a decrease in their total firing rate. This illustrates a mechanism of timing or 'gating' of cortical cell firing by the unspecific system which may have important functional implications. Verzeano *et al.* (85) have come to a different conclusion with regard to barbiturate spindle bursts recorded with microelectrodes in unspecific thalamic nuclei. They found a close relationship between spikes and waves and believed that the waves of the spindle bursts in the thalamus might represent positive after-potentials. A lack of consistent relationship was found, however, between unit spikes and convulsive waves induced by pentylenetetrazol (Metrazol) or picrotoxin.

THALAMIC DISTRIBUTION OF UNSPECIFIC PROJECTION SYSTEM

The thalamic distribution of the unspecific projection system was originally identified with the cells and fibers found within the internal medullary lamina of the thalamus, including a caudal expansion into the n. centrum medianum. The intralaminar cells do not show retrograde degeneration following neocortical lesions in the same manner as do the cells of specific thalamic nuclei so that they have long been considered not to have cortical projection fibers.[2]

[2] Degenerative changes of a minor character have been shown by Nashold *et al.* (60).

They have been considered to represent an intrathalamic association system, interconnecting various specific nuclei within the thalamus, but without direct connections with the cortex.

The nucleus centrum medianum, which is a relatively large structure in higher mammals, has been shown to have direct projections to the striatum (putamen) but not to the cerebral cortex, according to anatomical studies (21, 25, 26, 51, 52, 65, 66). Nevertheless the rostral pole of this nucleus regularly produces widespread cortical recruiting responses when stimulated repetitively. This has suggested that recruiting responses may be conducted to the cortex via the striatum or by a striatothalamic system (25, 26, 51, 52, 75, 82).

Both anatomical and physiological studies have suggested to some authors (52, 80) that recruiting responses reach the cortex by means of intrathalamic connections with specific nuclei and then are conducted with synaptic delay over specific projection fibers to the cortex. Such connections would be principally with the association nuclei of the thalamus, projecting to frontal and temporoparietal cortical association areas and not to sensory receiving areas, according to Starzl & Magoun (76) and others (52, 80).

Physiological studies have consistently shown that recruiting responses are less prominent or even absent from sensory receiving areas of the cortex and are especially hard to demonstrate in visual and auditory receiving areas. This has been shown, however, when stimulating the centrum medianum or mesioventral portions of the intralaminar system. If there exists a topographical organization within the unspecific system, there may be other portions of it more directly related to sensory areas. The close interconnections within the system have given the impression to some investigators that it responds in an all-or-none manner with a fixed pattern of cortical projection to only 'association' and motor areas of the cortex (80).

More recent anatomical and physiological studies have served to clarify some of these problems, although much has still to be learned about the details of the manner in which the unspecific projections reach all areas of cortex.

The independence of the unspecific projection system from specific thalamic nuclei has been proved by recording recruiting responses from each cortical area, including the sensory areas, following complete destruction of the thalamic nucleus known to have specific connections with a particular cortical area (31). For example, after finding a portion of the thalamic reticular system which produced good recruiting responses in the visual area (*VA* in fig. 4), the lateral geniculate body was completely destroyed by coagulation and recruiting responses demonstrated to be unaffected or increased from the same point of the visual cortex (fig. 5).

Similar results were obtained for auditory and somatic sensory areas following destruction of the medial geniculate and the n. ventralis posterior, respectively. It was remarkable that recruiting responses appeared of larger amplitude in all sensory areas after destruction of their respective thalamic relay nuclei. This suggests a competitive interaction between the specific and unspecific projection systems for the control of cortical electrical activity in sensory areas. Such an interaction was clearly demonstrated in later studies by Jasper *et al.* (43) who established again the existence of independent unspecific projections to sensory receiving areas in the cat.

It is now quite clear that the pathways of the unspecific projection system to all cortical areas need not pass via specific projection nuclei. There may still be additional connections with specific thalamic nuclei, but these are not essential for the mediation of the recruiting response. The effects of stimulating the thalamic reticular system are more difficult to demonstrate in sensory receiving areas of the cortex, most difficult in auditory and visual areas.

The extent of the thalamic reticular system, as determined by stimulation points yielding recruiting responses, includes structures other than those commonly included in the intralaminar system of nuclei. These areas are shown stippled in diagrammatic cross sections of the thalamus of the cat in figure 6. It will be noted that only the rostral pole of n. centrum median yields recruiting responses while an additional area in the vicinity of the n. suprageniculatus has consistently given recruiting responses, especially in ectosylvian regions.

It has been shown by both anatomical and physiological methods that the conduction pathway from the centrum medianum extends forward in the mesioventral thalamus, penetrating the n. ventralis medialis and into the n. ventralis anterior, then into the rostral pole of n. reticularis. This appears to be a mixed system of short multisynaptic connections and fibers. Unspecific fibers are particularly dense in the ventral third of the n. ventralis anterior, as shown by the double cross hatching of this region in figure 6.

Beginning in the n. centralis unspecific fibers and multisynaptic pathways extend dorsally into the

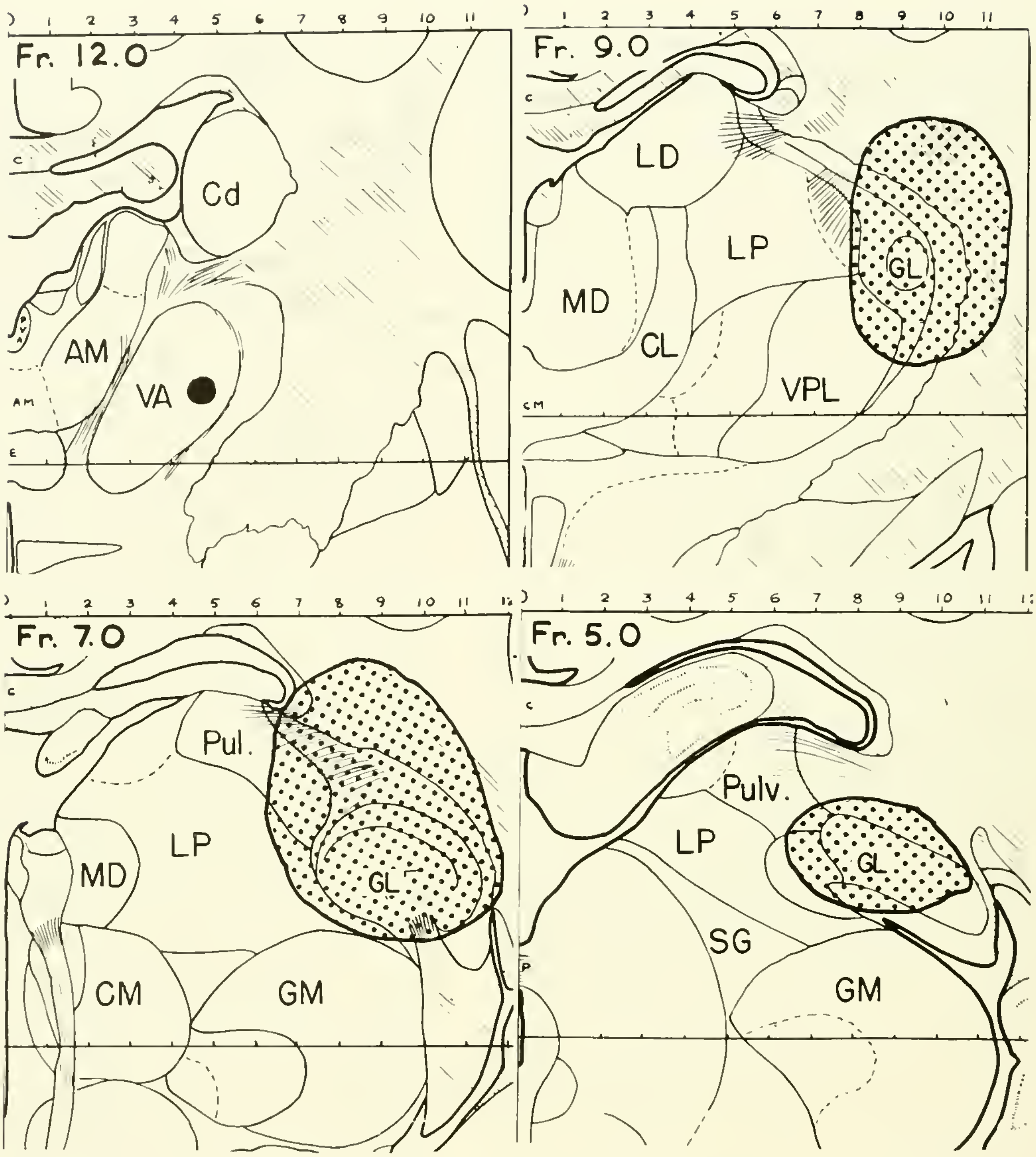

FIG. 4. Diagram of site of electrical stimulation at stereotaxic frontal plane 12 which produced good recruiting responses in the visual cortex as shown in fig. 5. The lesion produced by coagulation and intended to destroy the lateral geniculate body completely is outlined in the diagrams of frontal planes 9, 7 and 5. [From Hanbery & Jasper (31).]

limbs of the intralaminar system and the dorsolateral portion of n. ventralis anterior and reticularis. The dorsolateral portions show preferential conduction to more posterior areas of the cortex, while the medioventral portions show a dominant projection to frontal and mesial cortical areas. Using threshold local stimulation, a definite topographic organization can be shown, although it is a rather labile one, with con-

duction of recruiting responses readily from one part to another.

The extent to which the nucleus reticularis of the thalamus participates in the unspecific projection system has been the subject of some controversy. Rose (72, 73) proposed that this nucleus, with its caudal extension as a shell around the thalamus, might well contain many of the cells of origin of the final common pathways of the unspecific projection system. A similar conclusion was reached by Hanbery & Jasper (31), and by Hanbery *et al.* (30) based upon physiological and anatomical studies. In these studies it was shown that recruiting responses can be obtained from the thin posterior extension of n. reticularis, but that they are then more restricted to a limited cortical distribution, as might be expected if the final distribution of unspecific projections were via cells and fibers in this nucleus.

Anatomical and physiological studies (2, 60, 62) have also shown a more important rostrally-projecting pathway passing through the anterior limb of the internal capsule, just beneath and partially within the border of the head of the caudate nucleus. Some of these fibers terminate in the caudate nucleus, a fact which has led some authors to conclude that all unspecific fibers were relayed to the cortex via the caudate. Such a conclusion is not supported by physiological or anatomical evidence when care is taken to distinguish between the caudate nucleus proper and fibers of passage in the adjacent internal capsule (30, 60).

Further anatomical studies are necessary, combined with electrophysiological observations, before the exact nature and distribution of the final common pathway of the unspecific thalamic projection system is thoroughly understood. It would seem from present evidence that, although recruiting responses are obtained in the caudate nucleus and they can be obtained in the cortex upon stimulation of the caudate, the caudate nucleus is not an essential relay station in the thalamocortical conduction pathway of the unspecific projection system. Cortical recruiting responses may be of shorter latency than those simultaneously recorded in the caudate, and destruction of large portions of the caudate, sparing adjacent fibers of the internal capsule, has little effect upon thalamocortical recruiting responses. However, there is an intimate relationship between the striatum and the unspecific system as well as with other subcortical structures.

More recent anatomical studies have largely confirmed this conception of the intrathalamic organiza-

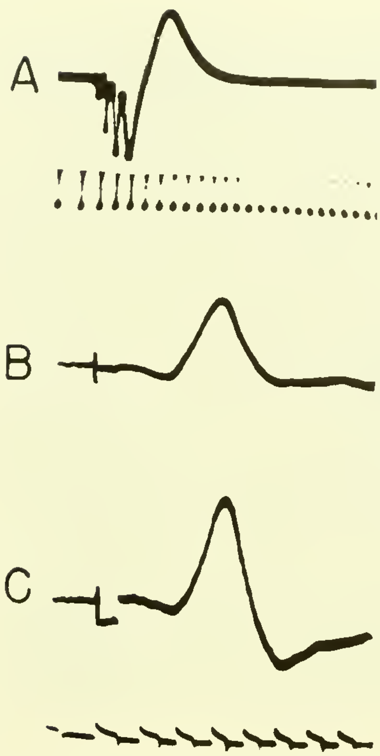

FIG. 5. Oscilloscope tracings of: *A*, specific visual evoked potential in response to a single shock to the lateral geniculate body (time line intervals, 2 msec.); *B*, recruiting potential from the same recording electrodes in the visual cortex response to stimulating nucleus ventralis anterior as shown in fig. 4; and *C*, recruiting response from same electrode site in the visual cortex after destruction of the lateral geniculate body as shown in fig. 4. Time line intervals, 10 msec. [From Hanbery & Jasper (31).]

tion of the unspecific projection system (44, 64). In addition important corticofugal projections into the thalamic as well as the brain-stem reticular system have been demonstrated (27, 41, 63), as well as projections from the cerebellum (Sprague, J. M., personal communication).

There appears to be a close relationship between the rhinencephalon and the thalamic recruiting or unspecific system. Certain of the nuclei known to be related to portions of the rhinencephalon (e.g. n. reuniens and anteromedialis) regularly produce widespread cortical recruiting responses. It has also been shown by Nauta that the hippocampus has many projections into the intralaminar nuclei of the thalamus (61). Unspecific thalamic projections have also been shown to the olfactory bulb (4).

Finally it may be necessary to point out that the so-called 'unspecific' thalamic projection system is actu-

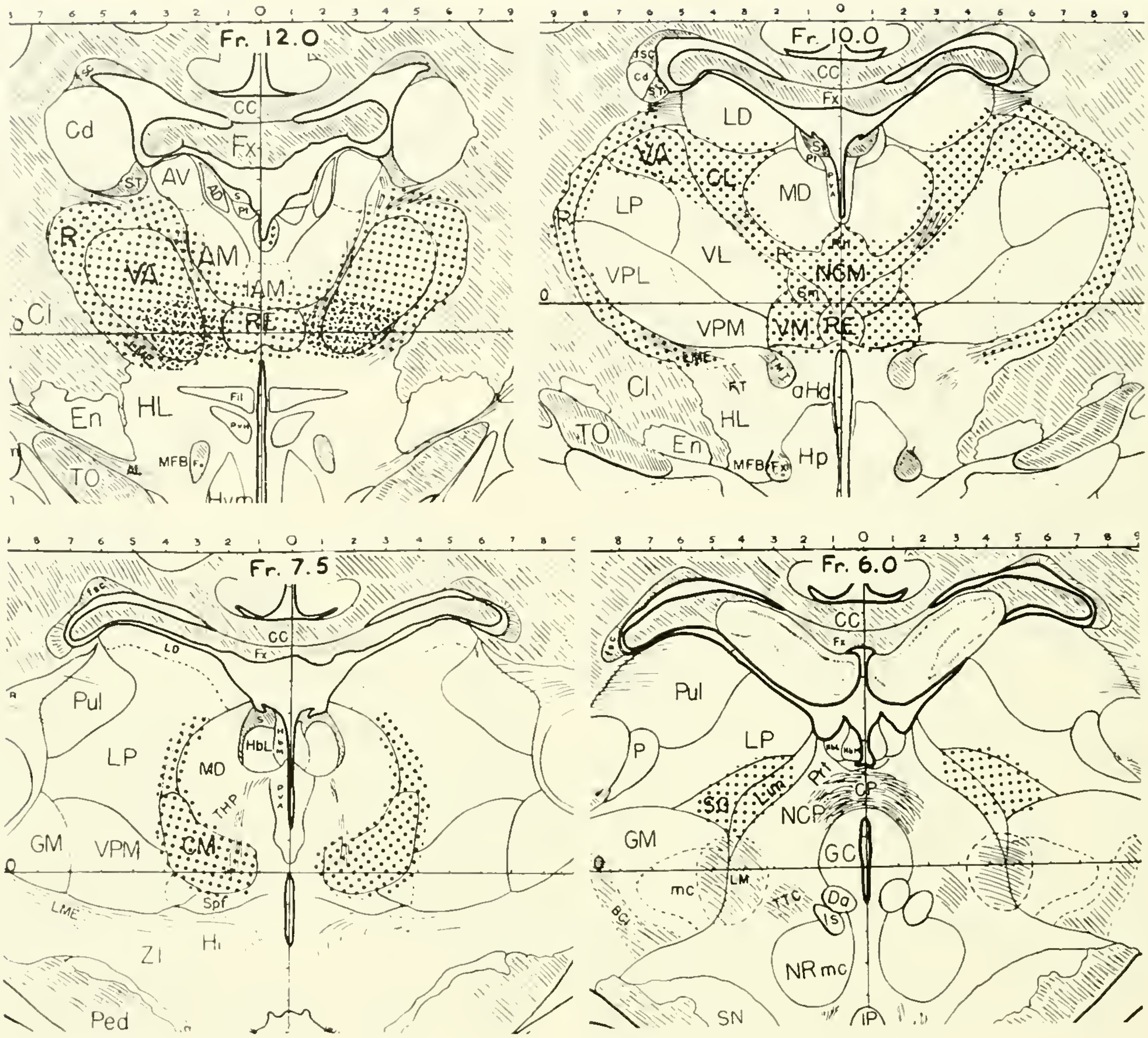

FIG. 6. Diagram of the thalamic reticular system as determined by *stippled areas* showing recruiting responses to local repetitive stimulation in the cat. Cross sections of stereotaxic frontal planes 12, 10, 7.5 and 6 are shown. The *double stippling* in the ventral portion of nucleus ventralis anterior indicates the region where rostrally conducting pathways are most dense.

ally a very definite and distinct ('specific') ganglionic organization of cells and fibers. When searching for it in the thalamus with a small bipolar stimulating electrode, using weak electric currents (the threshold is of the order of 2 to 4 v. for 1 msec. pulses), one finds that movement of the electrode only a fraction of a millimeter will suddenly cause large responses to appear which were absent before. It is not, therefore, a system of neurons diffusely distributed throughout the thalamus. It cannot be activated by stimulating within sensory relay nuclei nor from within other specific thalamic nuclei with the exception of certain border zones mentioned above. The terms 'unspecific' or 'diffuse' applied to this system may be misleading. These terms refer particularly to the widespread distribution of cortical responses, with only a loose regional topographical organization, in contradistinction with the relatively restricted local projections of different portions of specific nuclei. The thalamic distribution is also extensive, but not diffuse.

INTERRELATIONS BETWEEN SPECIFIC AND UNSPECIFIC PROJECTION SYSTEMS

Interrelation between specific and unspecific projection systems occurs at three levels: *a)* by means of collaterals from the principal sensory pathways, *b)* intrathalamic connections from intralaminar to specific thalamic nuclei and *c)* overlapping projections in almost all areas of the cerebral cortex. Corticofugal projections provide a fourth means of interaction between specific and unspecific systems.

The collateral fibers from sensory pathways (visual, auditory and somatic) converge into the reticular network of the centrum medianum and other intralaminar nuclei in a manner similar to that described for the brain-stem reticular system in Chapter LII by French in the present work. This is a relatively unspecific activation since little if any clear modality specificity has been demonstrated (27, 29, 53, 55, 78, 79). The longer latency, variability and adaptation of evoked potentials in the thalamic reticular system, when compared with responses in sensory relay nuclei, suggests a synaptic system with different properties and possibly also some difference in the type of fibers in sensory pathways which terminate in the thalamic reticular system.

The anatomical studies of Nauta & Whitlock (62), using a special silver impregnation method for axons and terminals, has shown that numerous fibers leave the main course from the centrum medianum forward in the thalamus to terminate in various specific thalamic nuclei along the way. A recruiting response can also be recorded from lateral thalamic nuclei in response to stimulation of the centrum medianum. The importance of these intrathalamic connections has yet to be determined. Even though they are not essential to the cortical distribution of recruiting responses, they may still play a significant role in thalamic integrative mechanisms.

In cortical sensory receiving areas it may be hard to demonstrate recruiting responses, as discussed above, due to competition with impulses arriving over specific projection fibers. With paired stimulation, alternating shocks to unspecific and specific systems, it is possible to demonstrate definite interaction of recruiting waves with the surface-negative component of the specific evoked potential complex in sensory areas (40, 81). Less effect can be demonstrated upon the initial surface positive phase of the specific complex. An example of such interaction in the visual cortex is shown in figure 7. Interaction appears to occur mainly, though not exclusively, after the volley of sensory impulses has passed the first cortical synapses and is being propagated into the dendritic network of the cortex.

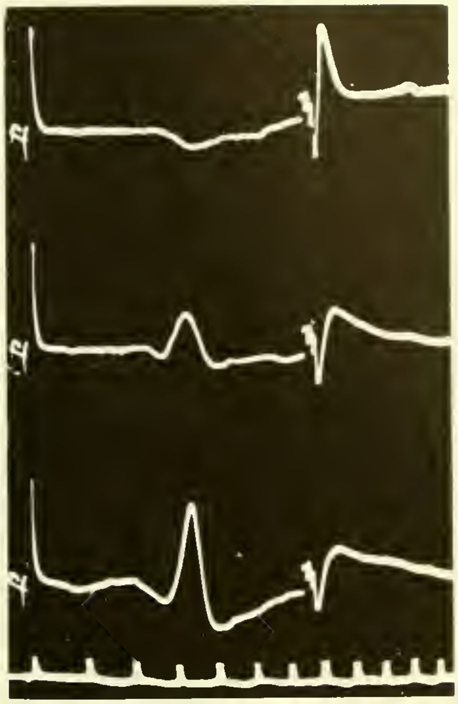

FIG. 7. Oscilloscope records of recruiting and specific evoked potentials from the visual cortex obtained simultaneously by repetitive stimulation with paired shocks. The initial shock was applied to the nucleus ventralis anterior followed by a test shock to the lateral geniculate body 62 msec. later. Note the reciprocal relationship between the variations in the recruiting wave and the amplitude of the surface-negative component of the specific evoked potential. Time line intervals, 10 msec. [From Jasper & Ajmone-Marsan (40).]

However, with microelectrodes, it has been shown that unspecific projections may modify the excitability and repetitive discharge of neurons which are fired with short latency in response to specific afferent volleys (46). Also rhythmic sensory after-discharge can be blocked completely by rapid stimulation of the thalamic reticular system. Therefore activity in the unspecific system may exert an effect upon the response of sensory cortex by *a)* modifying the initial cortical neuronal discharge, *b)* blocking, facilitating or timing the elaboration of impulses throughout the different layers of the cortex, and *c)* modifying the prolonged aftereffects of a sensory volley.

We do not know how these electrophysiological changes may be related to subjective sensation or perception, although possible relationships have been suggested (10, 47).

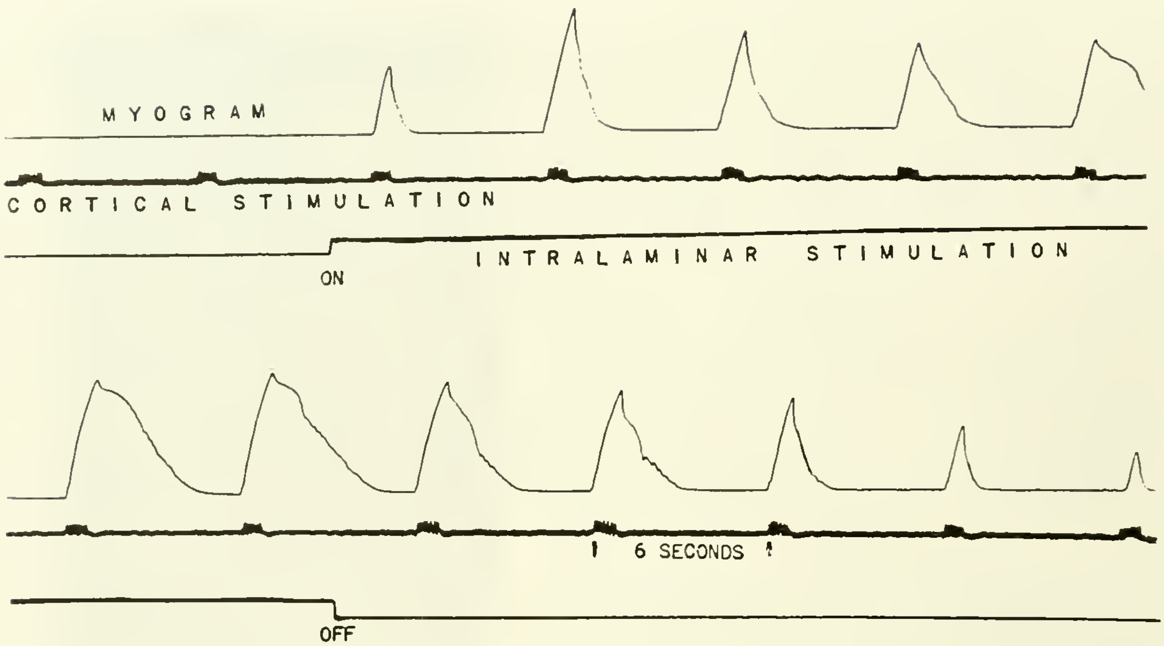

FIG. 8. Facilitation of cortically-induced movements in the cat (lightly anesthetized with pentobarbital) during intralaminar stimulation. [From Jasper (38).]

In the motor system it was first shown that cortically-induced movements could be facilitated markedly by rapid stimulation of the intralaminar system of the thalamus (38). The facilitation outlasted the period of stimulation by 20 to 30 sec., as shown in figure 8. Some of this facilitating effect remained after removal of the motor cortex, as shown by stimulation of the white matter beneath, so that this may represent largely a descending action upon spinal motor centers.

Brookhart & Zanchetti (12) have failed to show any effect of recruiting waves upon the activation of pyramidal cells, as recorded by means of electrodes directly in the tract at the level of the decussation (see fig. 9). Recruiting waves are often of large amplitude in the motor cortex, so that it would be surprising if they did not have some effect upon motor cortical function. Some relationship has been reported by Arduini & Whitlock (6). A definite relationship to spontaneous 'spindle' bursts was shown by Whitlock *et al.* (86) as well as by Brookhart & Zanchetti who also showed a clear relation between pyramidal discharge and augmenting waves in the motor cortex in response to stimulation of the n. ventralis lateralis of the thalamus. It is apparent that there are multiple rhythmic systems in the cortex and thalamus which may be dissociated and may have different functional significance (11).

Repetitive stimulation of specific thalamic nuclei at frequencies between 6 and 12 per sec. gives rise to local incremental responses simulating a recruiting response. These were called 'augmenting responses' by Morison & Dempsey (24, 58). They are distinguished by their location in the area of known projection of the specific system and by the short-latency surface-positive evoked potential complex which initiates each successive response. It is the surface-negative component which shows the greatest augmentation, and there may be waxing and waning in amplitude in a manner very similar to that observed for recruiting responses. It would seem that similar cortical elements and mechanisms of summation must be involved in both recruiting and augmenting responses, but this is not always true. It may even indicate that some unspecific cortical afferents, predominantly axodendritic, may also originate in specific thalamic nuclei, as suggested by the anatomical studies of Nauta & Whitlock (62). The longer latency of the true recruiting response may be due to multisynaptic circuits in the thalamic reticular system (5), while summation and delay in the augmenting response may be largely of cortical origin. Considerable delay may be accounted

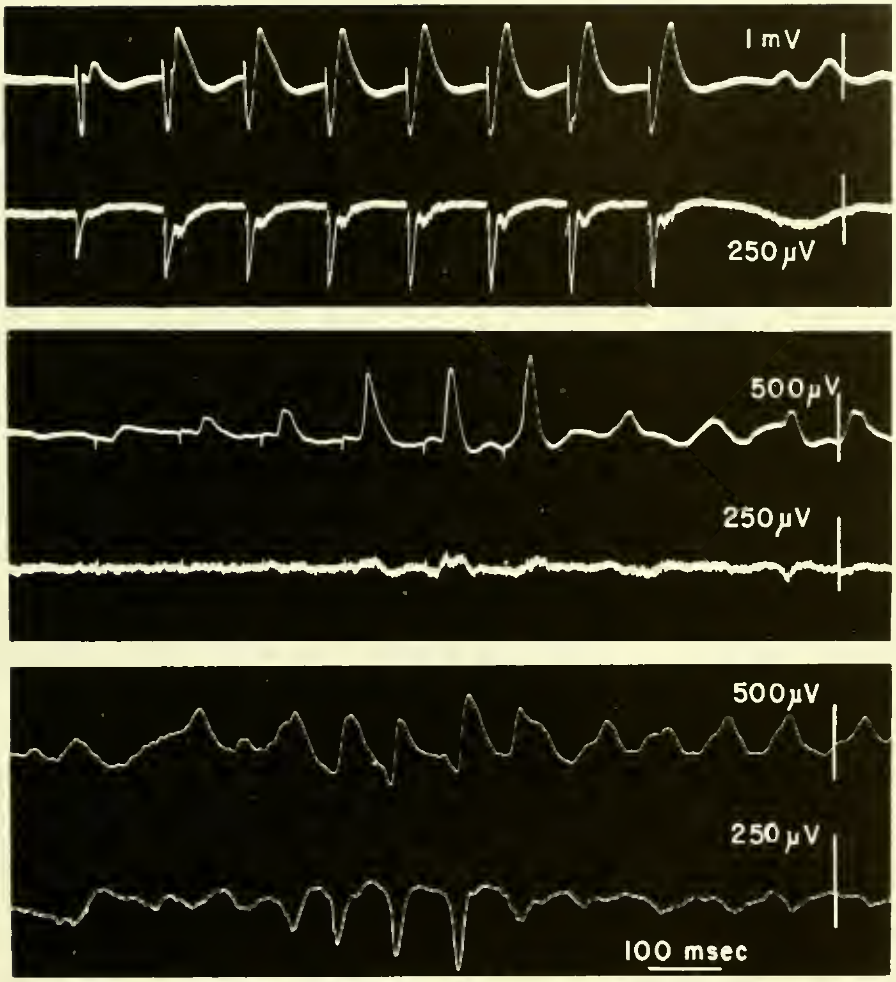

FIG. 9. Simultaneous recordings from the anterior sigmoid gyrus (*upper trace*) and medullary pyramid (*lower trace*). *Top:* Augmenting responses initiated in an unanesthetized cat by stimulation of n. ventralis lateralis; note the 'relayed' pyramidal volleys. *Middle:* Similar recordings from another preparation, recruiting response initiated by stimulation of n. reuniens; note the stability of the pyramidal recording. *Bottom:* Recordings taken during a spontaneous spindle burst in an unanesthetized cat with mesencephalic thermocoagulation; note the relayed spindle waves in the pyramidal recording. [From Brookhart & Zanchetti (12).]

for also if the unspecific fibers are small, unmyelinated and with slow conduction velocity.

Under certain conditions it is possible to show a remarkable degree of independence between augmenting and recruiting waves in the same area of the cortex, as was demonstrated by Brookhart & Zanchetti (12). Augmenting and recruiting responses may be readily confused in experimental studies since it is often hard to avoid stimulation of both specific and unspecific thalamic fibers at the same time. The augmenting responses are not as closely related to the spontaneous spindle bursts as are recruiting waves (56) since spindle bursts may appear intermingled with augmenting waves while they are usually more completely driven by unspecific thalamic stimulation. The augmenting responses are probably more closely related to the neuronal systems of the local sensory after-discharge (15).

There may be a more intimate interrelationship between specific and unspecific projection systems in association areas of the cortex, but the details of this relationship have yet to be worked out.

RELATION BETWEEN THALAMIC AND BRAIN-STEM ASCENDING RETICULAR ACTIVATING SYSTEMS

It seems clear that a considerable proportion of these ascending activating effects obtained from the basal diencephalic and midbrain portions of the reticular system are mediated to the cortex by means of the thalamic reticular system (53). As has been stated above, the spontaneous rhythmic activity of the cortex can be blocked, producing an activation pattern, by rapid stimulation within either the thalamic or the midbrain portions of the ascending reticular systems.

Recruiting responses obtained from stimulation of the intralaminar portions of the thalamus can also be blocked completely by simultaneous more rapid stimulation of the midbrain reticular system (59). Also recruiting responses are not readily obtained in an animal which shows the activation pattern in the cortex due to arousal by sensory stimulation when in the unanesthetized state. These observations demonstrate a close functional relationship between the brain-stem and thalamic reticular systems.

It has also been shown that large bilateral lesions produced by coagulation of the anterior portion of the thalamic reticular system result in unresponsiveness of animals quite similar to that produced by lesions of the midbrain reticular system (28, 48, 49). There may be some qualitative difference here however in that the profound depths of coma produced by midbrain lesions do not seem to be reproduced as completely in all cases by lesions within the anterior portion of the thalamic reticular system.

Differences between the cortical activation produced at thalamic or midbrain levels of activation should be pointed out however. In the first place, the recruiting response is not readily obtained by stimulation of the midbrain reticular system and usually requires stimulation within the thalamus.[3] The prolonged activation of the animal with the typical change in cortical electrical activity obtained by stimulation of the midbrain reticular system, or of the basal diencephalon, is not readily produced by rapid stimulation in the anterior portion of the thalamic reticular system.

The blocking of spindle bursts in the electrical activity of the cortex occurs only for a brief period of time, sometimes not outlasting the stimulus itself, when the thalamic system is being stimulated. Prolonged blocking of rhythmic cortical activity however, is readily produced, lasting for 30 sec. to several minutes, following stimulation of the midbrain reticular system in the unanesthetized animal.

It has been shown that cortical activation is of two forms, one of rapid onset and brief duration, and another of slow onset and prolonged duration. The former has been called the phasic activation system and the latter the tonic system. It now seems clear that the tonic activation system lies in the basal diencephalon and midbrain and has many properties distinct from the thalamic system. The phasic type of rapid but short duration arousal seems to be characteristic of the thalamic system. The tonic activation system of the brain stem is particularly sensitive to epinephrine, and it may well be that the tonic phase of activation from this area is largely due to the humoral aspect of activation of the brain with cells sensitive to this type of activation only in the diencephalon or hypothalamus and in the upper midbrain, but not in the thalamic portion of the reticular system (74).

There may be also differences in the effects of stimulating the thalamic reticular system upon behavior in the unanesthetized preparation. There is some evidence that diminished responsiveness or even sleep-like states may be produced from stimulation of the thalamic reticular system, as in the so-called 'arrest reaction' of Hunter & Jasper (35) or the sleep reaction of Hess (32, 33, 34). The intense excitement of an animal with attack or fear responses is not obtained from stimulation of the thalamic reticular system but requires stimulation either of the posterior hypothalamus or upper midbrain. It has recently been shown by Akimoto *et al.* (3) that repetitive stimulation at 5 to 10 per sec., producing a high degree of synchronous activity throughout the brain, results in sleep, while stimulation at more rapid frequencies causing desynchronization of cortical activity may result in an awakening reaction in unanesthetized animals with electrodes implanted in the intralaminar portion of the thalamus.

Another important difference between the brain-stem and the thalamic reticular system is that of topographical organization. Very little evidence for any topographical organization can be shown at the level of the hypothalamus or midbrain. There is some tendency for activating influences to be most effective on rostral cortical areas in frontal and motor regions, but in general the effects are quite generalized. In the thalamic system, on the other hand, different points within the system seem to have a different pattern of cortical projection. This is not a rigid topographical organization and there are many close interrelationships present, but it seems likely that there are portions of a system which can regulate the electrical activity of limited areas of the brain without affecting the cortex as a whole.

This capacity for some degree of localized activation would suggest functional properties of the thalamic system of a more highly organized character related to specific or different cortical functions rather than to generalized arousal or activation of the brain

[3] Evarts & Magoun have recently shown that a recruiting response can be obtained under certain conditions with implanted electrodes in the brain stem of the unanesthetized cat (26a).

as a whole. Due to this property of the thalamic system, it has been proposed by Jasper that the local activation processes of attention in the waking animal could be mediated, in part at least, by this system, although it is now known that processes of attention may also affect the specific projection systems, even at peripheral levels of sensory influx.

The participation of the thalamic reticular system in epileptic seizures of the type characterized by initial brief loss of consciousness ('petit mal') is still uncertain since the wave-and-spike pattern, which characterizes the EEG in patients with these seizures, is obtained by stimulating the intralaminar system only under very special conditions which are poorly understood (36). Seizure discharges are generally more readily transmitted over specific projection systems (77), although bilateral synchronization in cortical rhythms may be enhanced by epileptic lesions in the unspecific thalamic nuclei (69). It appears that both thalamic and mesencephalic portions of the reticular system may be involved in the central pacemaking circuits of the petit mal attack, and a certain general susceptibility of the cortex to this type of response may also be involved. This matter is considered further in Chapter XIV by Gastaut & Fischer-Williams in this work.

SUMMARY AND CONCLUSIONS

The unspecific thalamocortical projection system is composed of a closely interconnected multisynaptic network of neurons extending largely through the intralaminar portion of the thalamus with rostral direction of conduction toward the anterior portion of the thalamus where connections are formed with the reticular nucleus and the n. ventralis anterior for the origin of the major projection systems to widespread areas of the cortex. Important relationships to the striatum are present, although the final common pathways for cortical projection are as yet uncertain. Some may originate in the n. reticularis of the thalamus.

This projection system bears a very close relationship to certain components of the spontaneous electrical activity of the cortex and can regulate this activity either by timing it into rhythmical sequence or by arresting spontaneous rhythmical activity. The recruiting response, which is characteristic of this sytem, participates in timing rhythmic activity which is inherent in both the cortex and the thalamus. Such effects can be obtained on cortical activity independent of the specific projection pathways.

It seems likely that the synaptic termination of the unspecific system in the cortex is chiefly of the axodendritic type widely distributed throughout all layers of the cortex but under optimal conditions having its major effect on superficial layers.

This system forms a part of the ascending reticular activating system of the brain stem, although it possesses properties distinct from the portions of the reticular system in the hypothalamus and upper midbrain.

The functional significance of the unspecific thalamic system is not entirely clear. It seems to be the most important regulator of the spontaneous electrical rhythms of the entire cortex and be capable of some local effects in a loose topographical organization which may give it a more highly integrated function than might be attributed to lower portions of the reticular system. It seems to mediate a more rapid but shorter lasting cortical activation than do the more inferior portions of the reticular system. This is called the phasic type of activation as opposed to the tonic activation which is derived from hypothalamus and upper midbrain.

Studies of the interaction between the specific and nonspecific system in the thalamus indicate four types of interconnection: *a*) by means of collaterals from the principal afferent pathways directed medially into the intralaminar system, *b*) by collaterals from the intralaminar system terminating in specific thalamic nuclei, *c*) by convergence upon common neuronal systems in the cortex and *d*) by corticofugal projections reaching various parts of the thalamic reticular system.

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The intrinsic systems of the forebrain

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CHAPTER CONTENTS

There remains yet another type of integration which claims consideration, although to saddle it upon nerve may perhaps encounter protest. Integration has been traced at work in two great, and in some respects counterpart, systems of the organism. The physico-chemical (or for short physical) produced a unified machine from what without it would be merely a collocation of commensal organs. The psychical, creates from psychical data a percipient, thinking and endeavouring mental individual. Though our exposition kept these two systems and their integrations apart, they are largely complemental and life brings them co-operatively together at innumerable points. . . . For our purpose the two schematic members of the puppet pair which our method segregated require to be integrated together. Not until that is done can we have before us an approximately complete creature of the type we are considering. This integration can be thought of as the last and final integration.

But theoretically it has to overcome a difficulty of no ordinary kind. It has to combine two incommensurables; it has to unite two disparate entities. To take an example: I see the sun; the eyes trained in a certain direction entrap a tiny packet of solar radiation covering certain wave-lengths emitted from the sun rather less than 10 minutes earlier. This radiation is condensed to a circular patch on the retina and generates a photo-chemical reaction, which in turn excites nerve-threads which relay their excitation to certain parts of the brain, eventually to areas in the brain-cortex. From the retina onward to the brain the medium of propagation is wholly nervous; that is to say, the reaction can be subsumed as electrical. Some of this electrical reaction generated in the eye does not reach the brain-cortex but diverges by a side-path into nerve-threads which relay it to a small muscle, which by contracting prevents excess of light attaining the retina. The electric current propagated to the muscle activates the muscle. The chain of events stretching from the sun's radiation entering the eye to, on the one hand, the contraction of the pupillary muscle, and on the other to the electrical disturbances in the brain-cortex are all straightforward steps in a sequence of physical 'causation', such as, thanks to science, are intelligible. But in the second serial chain there follows on, or attends, the stage of brain-cortex reaction an event or set of events quite inexplicable to us, which both as to themselves and as to the causal tie between them and what preceded them science does not help us; a set of events seemingly incommensurable with any of the events leading up to it. The self '*sees*' the sun; it senses a two-dimensional disk of brightness, located in the 'sky', this last a field of lesser brightness, and overhead shaped as a rather flattened dome, coping the self, and a hundred other visual things as well. Of hint that this scene is within the head there is none. Vision is saturated with this strange property called 'projection', the unargued inference that what it sees is at a 'distance' from the seeing 'self'. Enough has been said to stress that in the sequence of events a step is reached where a physical situation in the brain leads to a psychical, which however contains no hint of the brain or any other bodily part. We cannot of course suppose that in the instance taken, the 'seeing the sun' breaks into a visual vacuum; in the waking day 'seeing' of some sort is always going on: on the physical side similarly electrical waves in the brain from one source or another must be practically unremitting during the waking day. The supposition has to be, it would seem, two continuous series of events, one physico-chemical, the other psychical, and at times interaction between them.

This is the body-mind relation; its difficulty lies in its 'how'. . . .

. . . Instead of, as is usual in physiology, leaving that impasse unmentioned, it seemed better to draw attention to it by the experimental observations in this book's final chapter.

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INTRODUCTION

FOR THE PAST CENTURY and a half, the 'mind-body' problem has been focused on the relationship between the functions of the cerebral mantle and mental processes. The question is often raised as to whether mental processes—especially 'complex' mental processes such as ideas, attitudes and thoughts—are radically (incommensurably) different from the physiological and the physical. With regard to elementary sensory and motor events (such as depressing a key when a light is flashed), the scientist proceeds upon the basis that psychological concepts (here the visual field) are inferred from observations and measurements of organism-environment interactions, interactions that can be specified by the use of physiological, physical and behavioral methods. Experimental evidence is presented here that more complex mental processes—such as thought, attitude, value—can also be studied in this manner: that environmental, organismic and behavioral referents for these processes can be specified—that, therefore, the difference between the psychological processes designated as complex and those designated as elementary is not a radical one.

Complex mental processes are most readily inferred from observations of problem-solving behavior. Those portions of the cerebral mantle devoid of any major direct connections with peripheral structures have been consistently linked with problem-solving processes and have, therefore, been of especial interest to students of the mind-body relationship. The designation 'association cortex' has obscured a considerable ignorance concerning the functions of these parts of the brain. The designation was framed within the empiricist tradition as this had evolved up to the latter part of the past century, and presupposes anatomical and physiological evidence for the notion of a transcortical reflex. Data are presented here upon which an alternative conception is proposed.

Definition of Intrinsic Systems of the Forebrain

The conception of an 'association cortex' stems from the fact that certain parts of the forebrain have obvious major direct connections with peripheral structures while others do not. This difference has been used by Rose & Woolsey (124) in a rigorous classification of the subdivisions of the dorsal thalamus—the forebrain structure which, as a whole, serves as the final discontinuity intercalated between peripherally initiated neural events and those of the endbrain. These investigators suggest the term 'intrinsic' for those portions of the dorsal thalamus in which no major extrathalamic, extratelencephalic afferents terminate. The intrinsic portions of the thalamus project to those sectors of the cerebral mantle usually referred to as 'association cortex.' As already noted, the term 'association cortex' has its disadvantages: 'association' makes the unsupported assumption that in these areas, convergent tracts bring together 'sensory' events transmitted from the 'receiving areas' of the brain. Throughout this presentation, therefore, the currently less loaded term 'intrinsic sectors' will be substituted for 'association cortex'; 'intrinsic systems' will be used when reference is made to the thalamic projection as well as to the related cortical area.

The key to an analysis of the functions of the intrinsic systems of the forebrain is obtained from a study of the organization of the mammalian thalamus. On the basis that some of the nuclear groups within the thalamus bear a fairly consistent relation to one another, an external portion and an internal core of the thalamus can be distinguished (59). The external portion is composed of the ventral, the posterior (lateral and pulvinar) and the geniculate nuclei (fig. 1). In carnivores and primates this external portion is, for a considerable extent, demarcated from the internal core of the dorsal thalamus by an aggregation of fibers, the internal medullary lamina and its rostral extensions surrounding the anterior nuclear group. The internal core of the dorsal thalamus may also be subdivided into three large groups: the anterior, the medial and the central (mid-line and intralaminar) nuclei.

Each of the major subdivisions (external and internal) may be further characterized according to the type of its nontelencephalic major afferents (fig. 2). Thus, the ventral and geniculate nuclei of the external division are the terminations of the large topologically discrete 'specific' afferent tracts (e.g. spinothalamic, trigeminal, lemniscal and the brachium conjunctivum, as well as the otic and optic radiations) of the somatic, gustatory, auditory and visual systems (144). Within the internal core, the anterior nuclei receive an input from the posterior hypothalamus through the mammillothalamic tract; the central nuclei receive nonspecific diffuse afferents by way of the reticular forma-

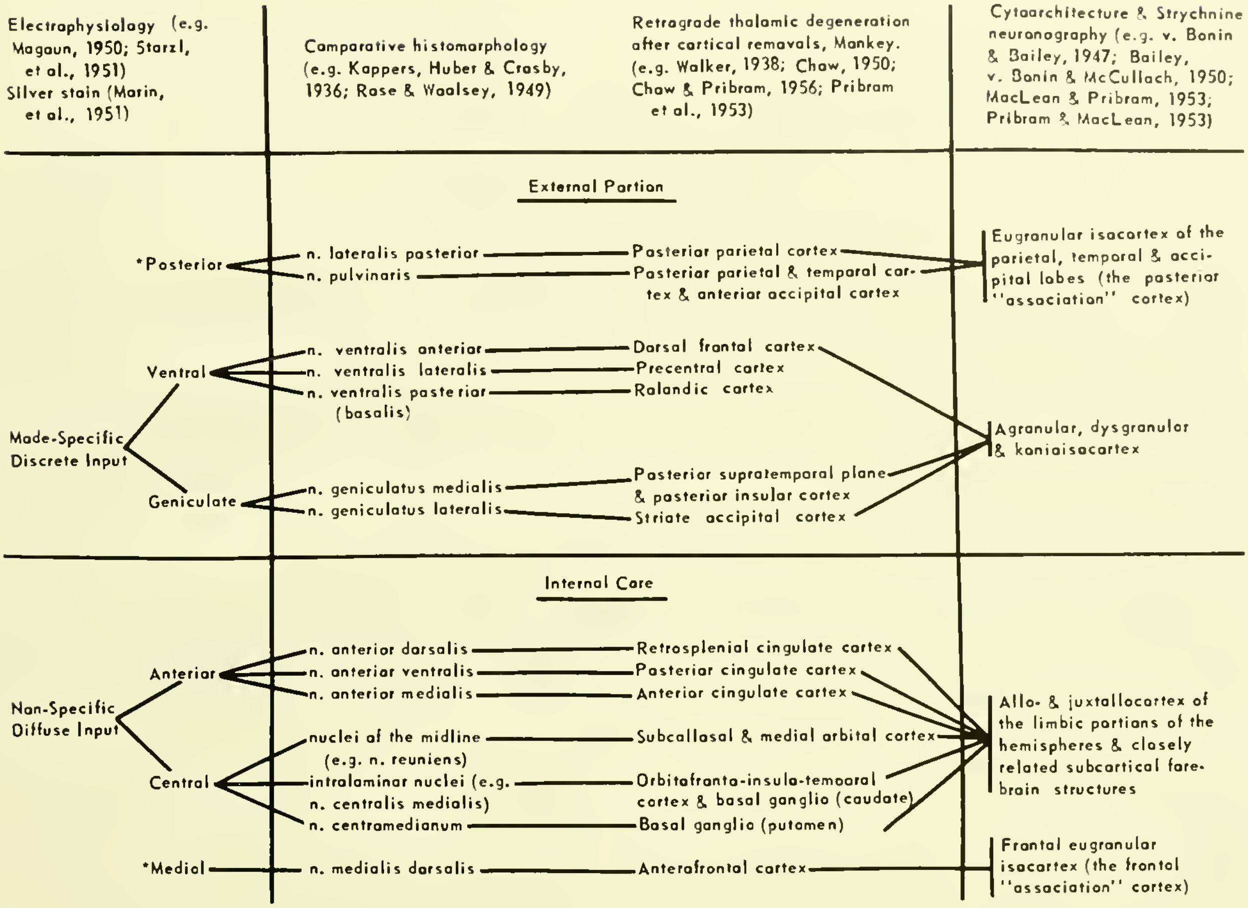


FIG. 1. Diagram of the distinctions between an internal core and an external portion of the forebrain. Examples of the techniques and particular studies invoked in making the classification are given in the *upper column*. As in any such classification, its heuristic value should not obscure its deficiencies. There is, of course, a multiplicity of forebrain systems, each of which partakes to a greater or less extent of the characteristics defining the internal core and those defining the external portion. In general, however, the nearer a system is to the central canal (or ventricular system) of the central nervous system, the greater the number of its 'internal core' characteristics; the further from the central canal, the greater the number of its 'external portion' characteristics. Also, the interaction of these various systems must not be ignored; this scheme is a restricted analysis and does not deal with such interactions.

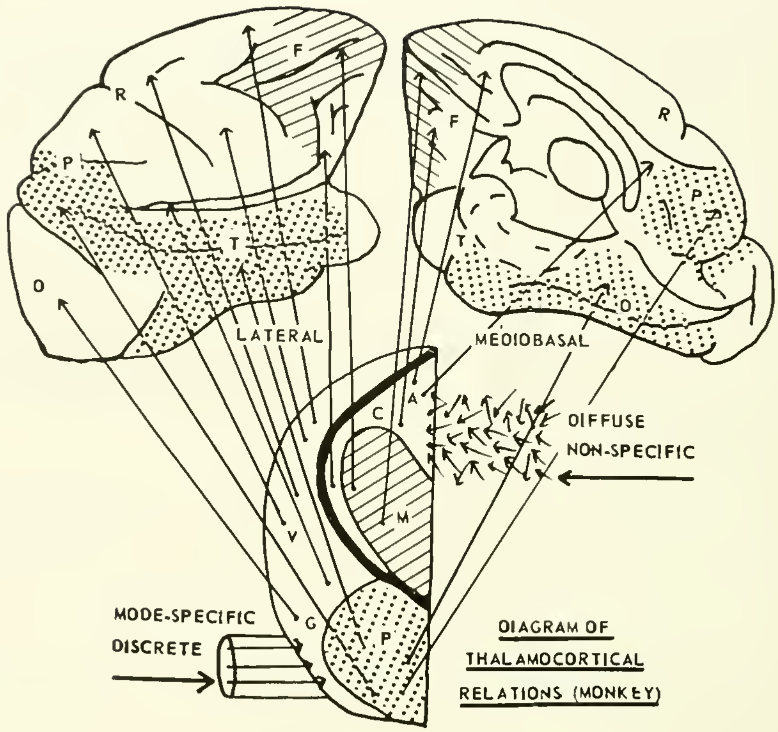
tion of the mesencephalon and, in addition, a probable input from the anteromedial hypothalamus (95, 96).[1] Thus the constancies of morphology in the mammalian thalamus reflect certain gross distinctions which can be made in the types of afferents to the forebrain.

The other two nuclear groups, the posterior in the external portion and the medial in the internal core, do not receive any such major extrathalamic afferents and, as noted above, are therefore classified as the 'intrinsic' nuclei of the thalamus (124). Important to the argument presented here is the fact that an intrinsic nucleus is assigned to each of the major thalamic divisions (see fig. 2).

The telencephalic projections of the external portion of the dorsal thalamus terminate in the dorsolateral and posterior cortex (figs. 1, 2). The termination of the telencephalic projections of the internal core is in the frontal and mediobasal portions of the

[1] In this respect, the classification presented here differs from that of Rose and Woolsey. These authors do not accept the evidence from silver-stained preparations as indicating a major extrathalamic, extratelencephalic input. Heuristically, such evidence is accepted here.

FIG. 2. Schematic representation of the projections from the dorsal thalamus to the cerebral cortex in the monkey. The *lower half* of the figure diagrams the thalamus, the *straight edge* representing the mid-line; the *upper half* of the figure shows a lateral and mediobasal view of the cerebral hemispheres. The *broad black band* in the thalamic diagram indicates the division between an internal core which receives a nonspecific diffuse input and an external portion which receives the modality-specific discrete projection tracts. The *stippled* and *crosshatched* portions represent the intrinsic systems: the medial nucleus of the internal core and its projections to the anterofrontal cortex; the posterior nuclear group of the external portion of the thalamus and its projections to the parietotemporooccipital cortex. The boundaries of the cortical sectors of the intrinsic systems are not sharp and as yet not precisely defined—thus, this diagram is to be read as a tentative approximation, based on currently available evidence. *F*, frontal; *R*, rolandic; *P*, parietal; *T*, temporal; *O*, occipital; *A*, anterior; *C*, central; *M*, medial; *V*, ventral; *G*, geniculate; *P*, posterior.



forebrain and includes the basal ganglia. Specifically, the ventral group of the external portion of the dorsal thalamus projects to the dorsolateral cortex of the frontal and parietal lobes (15, 144); the geniculate groups, to the lateral portion of the temporal and the posterior portion of the occipital lobe (144); the posterior nuclear group, to the remaining cortex of the parietotemporopreoccipital (P.T.O.) convexity (10, 15).

Within the internal core (figs. 1, 2), the medial nuclei project to the anterofrontal cortex (or orbitofrontal, as it has been called in subprimate mammals) (86, 112, 123, 144). The anterior and the central nuclei project to the medial and basal forebrain structures, the anterior nuclei to the cingulate areas on the medial surface of the frontal and parietal lobes (73, 86, 106, 113, 122, 125, 146); the central nuclei project (5, 20, 98, 105, 111, 124) to the anterior rhinencephalic and closely related juxtallocortical areas and basal ganglia [the second rhinencephalic system as defined by Pribram & Kruger (114)].

In summary, an intrinsic nuclear group and its projections is described for each of the major thalamic subdivisions: a posterior intrinsic system, related to the external portion of the thalamus and the dorsolateroposterior cerebral convexity; a frontal intrinsic system, related to the internal core of the thalamus and the frontomediobasal areas of the cerebral hemispheres.

NEUROBEHAVIORAL ANALYSIS OF POSTERIOR INTRINSIC SYSTEM

As already noted, the forebrain may conveniently be divided into two major portions, a dorsolateroposterior and an anteromediobasal. In primates each of these major portions contains intrinsic sectors: posterior intrinsic sectors (the classical sensory association areas) (108), and a frontal intrinsic sector (the classical frontal association area) (110). Neurobehavioral experiments performed during the past 25 years have shown these intrinsic sectors to be especially related to problem-solving processes (51, 107). The aim of this, and of the following sections, is to specify in detail this relationship.

An Experiment

A modified Wisconsin General Testing Apparatus (49) is used to test 12 rhesus monkeys in the solution of a complex problem. The monkeys are divided into three groups, two operated and one control, each containing four animals. The animals in one operated

group had undergone bilateral cortical resections in the posterior intrinsic cortex, and those in the other operated group bilateral cortical resections in the frontal intrinsic cortex some $2\frac{1}{2}$ years prior to the onset of the experiment (fig. 3); those in the control group are unoperated. In the testing situation these animals are confronted initially with two junk objects placed over two holes (on a board containing 12 holes in all) with a peanut under one of the objects. An opaque screen is lowered between the monkey and the objects as soon as the monkey has displaced one of the objects from its hole (a trial). When the screen is lowered, separating the monkey from the 12-hole board, the objects are moved (according to a random number table) to two different holes on the board. The screen is then raised and the animal is again confronted with the problem. The peanut remains under the same object until the animal finds the peanut five consecutive times (criterion). After a monkey reaches criterion performance, the peanut is shifted to the second object and testing continues (discrimination reversal). After an animal again reaches criterion performance a third object is added (fig. 4). Each of the three objects in turn becomes the positive cue; testing then proceeds as before—the screen separates the animal from the 12-hole board, the objects are placed randomly over three out of the 12 holes (with a peanut concealed under one of the objects), the screen is raised, the animal is allowed to pick an object (one response per trial), the screen is lowered and the objects are moved to different holes. The testing continues in this fashion until the animal reaches criterion performance with each of the objects positive in turn. Then a fourth object is added and the entire procedure repeated. As the animal progresses, the number of objects is increased serially through a total of 12 (fig. 5). The testing procedure is the same for all animals throughout the experiment; however, the order of the introduction of objects is balanced—the order being the same for only one monkey in each group.

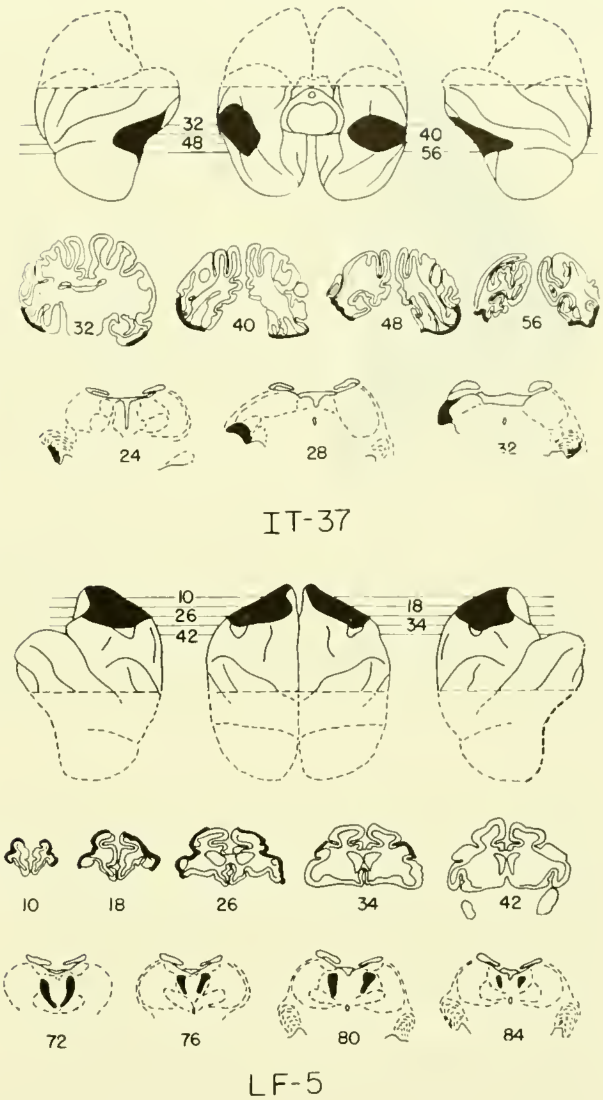
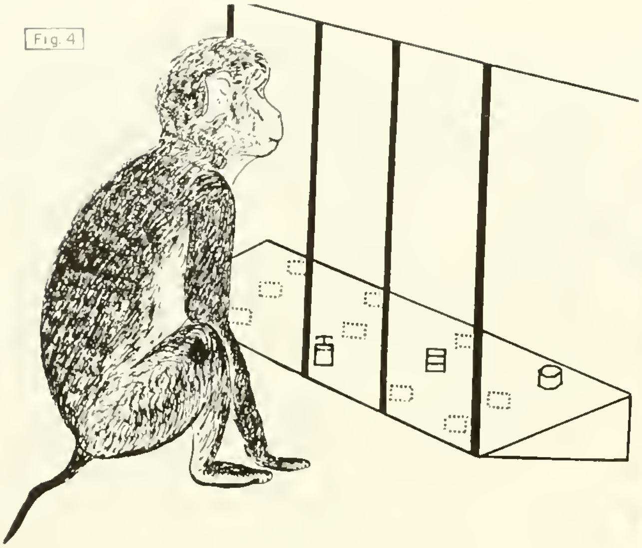
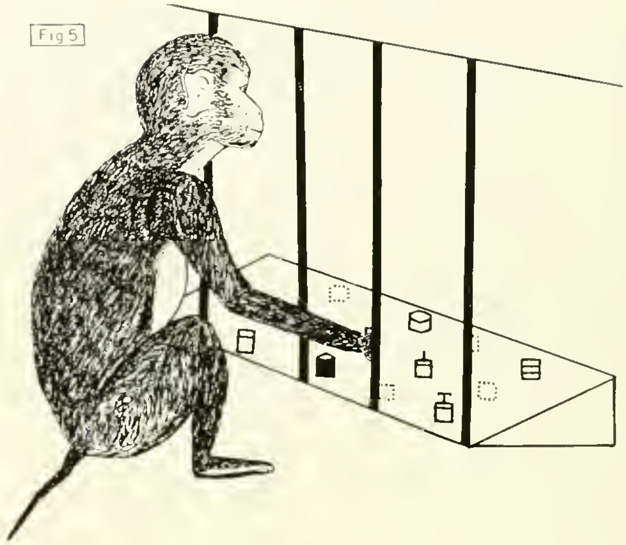


FIG. 3. Representative reconstructions and cross sections through the cortex and thalamus showing extent of the lesions in the posterior (*upper figure*) and frontal (*lower figure*) intrinsic systems. Cortical lesion and resulting thalamic degeneration shown in *black*.

Analysis of the problem posed by this experiment indicates that solution is facilitated when a monkey attains two strategies: *a*) during search—moving, on successive trials, each of the objects until the peanut is found; *b*) after search—selecting on successive trials the object under which the peanut had been found on the preceding trial. During a portion of the experiment, searching is restricted in animals with posterior intrinsic sector ablations, and selection of the object under which the peanut had been found on the previous trial is impaired by frontal intrinsic sector ablations. The effects of the posterior intrinsic sector lesion will be dealt with first.

Figure 6 graphs the averages of the total number of repetitive errors made by each of the groups in each situation. Comparison of figure 6 with figure 7, representing the repetitive errors made by each group in each situation during search, illustrates that the deficit of the frontally operated group is not associated with search (a result that is discussed below); however, the peak and general shape of the error curves





FIGS. 4 AND 5. Diagrams of the multiple object problem showing examples of the three and the seven object situations. Food wells are indicated by *dashed circles*, each of which is assigned a number. The placement of each object over a food well was shifted from trial to trial according to a random number table. A record was kept of the object moved by the monkey on each trial, only one move being allowed per trial. Trials were separated by lowering an opaque screen to hide from the monkey the objects as they were repositioned.

describing the performance of the control and posteriorly operated groups are similar whether total repetitive errors (fig. 4) or search errors (fig. 7) are plotted. In spite of the increasing complexity of the succeeding situation, the curves appear little different from those previously reported to describe the formation of a discrimination in complex situations (8, 130). Although one might a priori expect the number of repetitive responses to increase monotonically as a function of the number of objects in the situation, this does not happen. Rather, during one or another phase of the discrimination, the number of such responses increases to a peak and then declines to some asymptotic level (8, 130). Analysis of the data of the present experiment has shown that these peaks or 'humps' can be attributed to the performance of the control and posteriorly operated groups during the initial trials given in any particular (e.g. 2, 3, 4 · · · cue) situation i.e. when the monkey encounters a novel object. The period during which the novel and familiar objects are confused is reflected in the 'hump' (fig. 8). The importance of experience as a determinant of the discriminability of objects has been emphasized by Lawrence (75, 76). His formulation of the 'acquired distinctiveness' of cues is applicable here. In a progressively more complex situation, sufficient familiarity with all of the objects must be acquired before a novel object is sufficiently distinctive to be readily discriminated.

But there is a difference between the control and the posteriorly operated groups as to when the confusion between novel and familiar objects occurs. The peak in errors for the group with posterior lesions lags behind that for the controls—a result which forced attention because of the paradoxically 'better performance' of this group throughout the five- and six-cue situations (in an experiment which was originally undertaken to demonstrate a relation between number of objects in the situation and the discrimination 'deficit' previously shown by this group).

These paradoxical results are accounted for by a formal treatment based on mathematical learning theory: on successive trials the monkeys had to 'learn' which of the objects now covered the peanut and which objects did not. At the same time they had to 'unlearn,' i.e. extinguish, what they had previously learned—under which object the peanut had been and under which objects it had not been. Both neural and formal models have been invoked to explain the results obtained in such complex discrimination situations. Skinner (130) postulated a process of neural induction to account for the peak in errors—much as Sherrington had postulated 'successive spinal induction' to account for the augmentation of a crossed extension

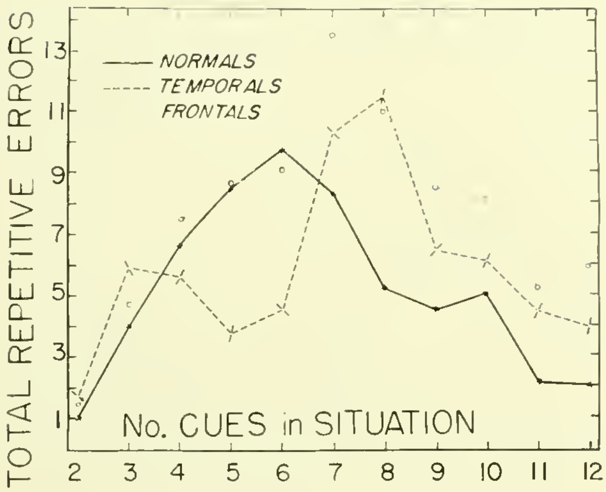


FIG. 6. Graph showing the average of the total number of repetitive errors made in each of the situations in the multiple object experiment by each of the groups: control animals (*Normals*); animals with posterior intrinsic sector lesions (*Temporals*); and animals with frontal intrinsic sector lesions (*Frontals*). A situation is defined by the number of objects in the problem and includes successions of trials. During each succession the peanut is consistently placed under one of the objects (cues). The succession is terminated when the monkey has moved the object under which the peanut is placed on five consecutive trials (criterion). (See also the legends to figs. 4, 5 and 10.) A repetitive error is made by a monkey when during a succession of trials he moves more than once an object other than the one under which the peanut is placed.

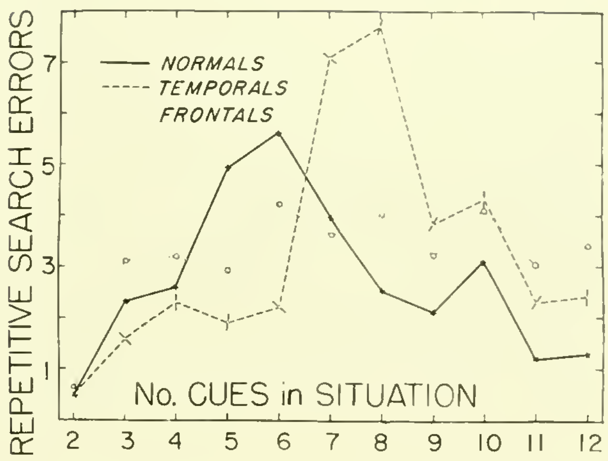


FIG. 7. Graph of the average of the number of repetitive errors made in the multiple object experiment by each of the groups during search (see legend to fig. 6). Search trials are those anteceding the first 'correct' response in a succession of trials, i.e. those anteceding the movement of the object (cue) under which a peanut has been placed. Note the difference between the location of the 'hump' in the graph of the normal controls and in that of the group with posterior lesions (*Temporals*).

reflex by precurrent antagonistic reflexes (such as the flexion reflex). Several of Skinner's pupils (24, 46a) have developed formal models. These models are based on the idea that both 'learning' (or 'conditioning') and 'unlearning' (or 'extinction') involve antagonistic response classes—that in both conditioning and extinction there occurs a transfer of response probabilities between response classes. This conception is, of course, similar to Sherrington's description of the interaction of antagonistic reflexes: ". . . *this* reflex or *that* reflex but not the two together." The resulting equations that constitute the model contain a constant which is defined as the probability of sampling a particular stimulus element (46a), namely the object, in the discrimination experiment presented here. This constant is further defined (Estes) as the ratio between the number of stimulus elements sampled and the total number of such elements that could possibly be sampled. This definition of the constant postulates that it is dependent for its determination upon both environmental and organismic factors. According to the model the rapidity of increase in errors in a discrimination series depends on this sampling ratio—the fewer objects sampled, the more delayed the peak in recorded errors. The paradox that for a portion of the experiment the group with posterior lesions performs better than the control group stems from the relative delay in the peak of the recorded errors of the operated group.[2] The model

[2] The actual model used to interpret the data analyzed here was developed by Green (46a) and is patterned after a model of discrimination learning proposed by Bush & Mostellar (8). The Green model takes its roots from a parallel model originated by Estes (24, 25). The general form of the model is derived from Estes' equations describing the conditioning and extinction processes:

$\bar{p}_n(S - I) = 1 - (1 - \bar{p}_0)(1 - \theta_1)^{\pi n}$ for conditioning to those elements which constitute occasions for reinforcement,

$\bar{p}_n(S' - I) = \bar{p}_0(1 - \theta_2)^{\bar{\pi} n}$ for extinction to those elements which are never occasions for reinofrcement, and

$$\bar{p}_n(I) = \frac{\pi\theta_1}{\pi\theta_1 + \bar{\pi}\theta_2} - \left[\frac{\pi\theta_1}{\pi\theta_1 + \bar{\pi}\theta_2} - \bar{p}_0\right](1 - \pi\theta_1 - \bar{\pi}\theta_2)^n$$

for the changes associated with intercept elements, i.e. those present on both reinforced and unreinforced occasions;

where

S represents the stimulus elements (objects) which are reinforced (have peanuts under them),

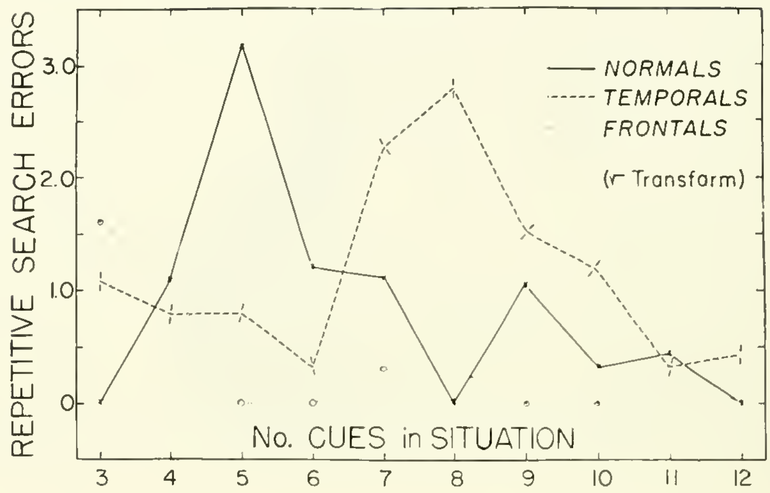


FIG. 8. Graph of the average of the number of repetitive errors made in the multiple object experiment during those search trials in each situation when the additional, i.e. the novel, cue is first added. Note that the peaks in errors shown in fig. 7 are accounted for by the monkey's confusion between novel and familiar objects as graphed here.

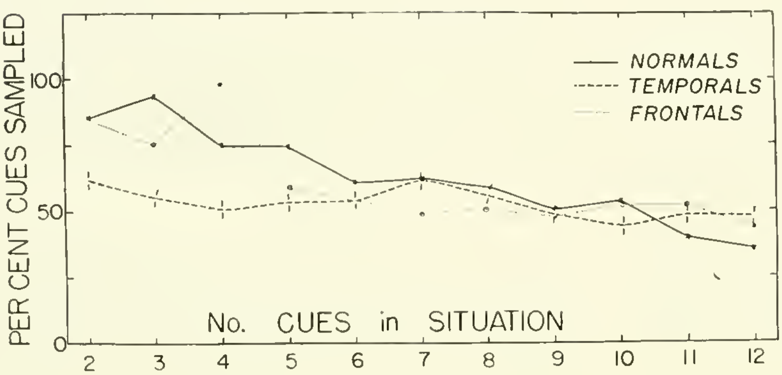


FIG. 9. Graph of the average of the per cent of the total number of objects (cues) that are sampled by each of the groups in each of the situations (see legend to fig. 6). To sample, a monkey had to move an object until the content or lack of content of the food well was clearly visible to the experimenter. As was predicted (see text), during the first half of the experiment the curve representing the sampling ratio of the posteriorly lesioned group differs significantly from the others at the .024 level [according to the nonparametric Mann-Whitney U procedure (84)].

predicts, therefore, that this operated group has sampled fewer objects during the early portions of the experiment. This prediction is tested as shown in the graph of figure 9.

The prediction is confirmed. The posterior intrinsic sector is thus established as one of the organismic variables that determine the constant of the model. As postulated by the model, the ratio of objects sampled

S' represents those stimulus elements which are not reinforced,

I represents the overlap between S and S' which expresses confusion when reinforcement is shifted from one to another object,

π represents the relative frequency of reinforced trials in the stimulus series,

$\bar{\pi}$ represents the relative frequency of nonreinforced trials in the stimulus series,

$\bar{p}_n$ represents the mean probability of response on the nth trial,

$\bar{p}_0$ represents the initial probability of response (operant level),

θ_1 and θ_2 represent the sampling ratios for reinforced and nonreinforced stimulus sets respectively, and

n denotes the number of trials.

It is assumed that the above equations are weighted directly as a function of the proportion of elements within the intercept and nonintercept subsets, such that

$$\bar{p}_n(S') = k'\bar{p}_n(S' - I) + (1 - k')\bar{p}_n(I)$$

In these experiments, then,

S' is the set of unreinforced stimulus elements (objects under which no peanut is located),

I includes among the subset of elements common to both reinforced and unreinforced trials those objects which 'recently' have had a peanut under them,

k' is the proportion of stimulus elements not common to both reinforced and unreinforced trials, and

$\bar{p}_n(S')$ is the mean probability of response on nonreinforced trials (probability of error responses) on the nth trial.

In the present experiment only the objects with no peanuts under them are considered since only one object at a time had a peanut under it. Thus the set of reinforced objects reduces to one, and the sampling ratio associated with it θ_1 is maximized with respect to the sampling ratio associated with the unreinforced sets, θ_2.

turns out to be more basic than the number of objects in the situation per se.

Review of Other Data

The lag in attaining the strategy to sample extensively shown by monkeys with posterior intrinsic sector lesions is correlated with other deficiencies in differentiation that follow such lesions. These deficiencies differ in some respects from those produced by lesions of the extrinsic (classical 'primary projection') systems, but the differences are subtle and have repeatedly eluded precise specification (116). The available data may therefore be briefly reviewed in a renewed attempt at such specification. *a*) Drastic bilateral removal of an extrinsic sector severely limits differentiative behavior in the modality and only in the modality served by that sector. The limitation affects practically all differentiations in the mode: thus, a monkey in which the occipital lobes have been removed reacts only to gross changes in the environment that affect the visual receptors—changes that can be ascribed to variations in total luminous flux (61). Comparably, drastic bilateral removal of a posterior intrinsic sector restricts differentiative behavior within the mode served by that sector, and only within that mode, but the limitation is not as severe as that produced by drastic removal of the extrinsic sector serving that mode (14, 107). *b*) Under some conditions, differentiation is unimpaired after drastic posterior intrinsic sector resection: for example, after such a removal, a monkey can catch a flying gnat in mid-air and can pull in a peanut which is beyond reach but attached to an available fine silk thread (0000 surgical). In these situations, as in situations that necessitate the opening of a single box or depressing of a single lever, the operated animal is indistinguishable from an unoperated control (108). *c*) Under other conditions, such as those in the experiment described above, differentiation is impaired after posterior intrinsic sector ablations. These conditions have in common the requirement that two or more separate responses be systematically related to the differences between the environmental events that determine the stimulus; i.e. alternatives are available to the organism, alternatives that are specified by environmentally determined stimuli. Such stimuli, for convenience, will hereafter be referred to as 'input' variables. Examples of the problems where impairment is found in the visual mode are: brightness, color, form, pattern, size and flicker discriminations (90–92); successive and simultaneous discriminations (116); successions of discriminations ('learning set') (12, 120); oddity discriminations (50); and matching from sample (50). Although the operated animals may perform 'normally' on particular problems within a problem group, decrement is found on other more 'difficult' problems in that group. Difficulty of problem is independently defined by the number of trials taken by naive unoperated animals to learn the problem. In most instances problem difficulty has also been related to differences between the physical dimensions of the objects, such as size discrimination (91), and to other determinants of the alternatives in the situation, including situational differences (116) and sampling in the multiple-object problem.

Analysis of Results

These then are the data. Extensive bilateral ablations of both extrinsic and posterior intrinsic sectors impair differentiative behavior, but differences between the impairments exist. Attempts to portray these differences are familiar. Neurologists have spoken of 'defective sensibility' and of 'agnosia' (33, 52), the latter often conceived as a disorder of memory. In so far as this distinction assumes an associationistic model of the functions of the intrinsic sectors, it gains little support from neurological or neuropsychological evidence (108). An alternate view can be proposed. Psychologists have spoken of 'existential discriminations' and 'differential discriminations' (57), or of 'sensibility' and 'intelligibility' (89), distinctions that are made on the basis of whether the organism's actions are determined by 'simple presence or absence' of input variables or by 'some more complex relationship' between these variables, such as the number of 'contextual alternatives' in the situation (88). The results of the experiment reported in this presentation warrant an attempt to pursue this conceptualization of the distinction by proposing a formal model of the interaction between the functions of the intrinsic and extrinsic sectors in differentiative behavior.

The defect in differentiative behavior that results from lesions of the extrinsic and posteror intrinsic sectors of the forebrain can be characterized by stating the variety of transformations of the input under which behavior remains invariant. Following extensive bilateral resections of the extrinsic sectors, behavior remains invariant under a great variety of transformations of the input. For instance, for these preparations, even brightness and size of luminant are multiplicatively interchangeable quantities (61), whereas differentiative behavior by organisms with

intact extrinsic sectors is invariant under much more restricted ranges of transformations of the input—such as differentiation in the case of contrast and contour (80), texture and acuity (39); continuous (orthogonal) projective in the case of position, distance, form and rigid motion (40, 41, 43).

The effects of lesions of the posterior intrinsic sectors can also be characterized usefully in this way. Differentiative behavior which remains invariant under still fewer transformations of the input is interfered with by such lesions. In the extreme, unique responses, i.e. 'absolute' differentiations, would be most affected.

Unique responses can occur only when both an 'absolute' unit and an 'absolute' reference point have been fixed. As indicated in the discussion of the results of the multiple object experiment, the mathematical learning theory provides an approach to the specification of these units and their referents. The fact that this mathematical device has proved so powerful a tool in the analysis of some completely unexpected effects of posterior intrinsic sector lesions lends support to its usefulness in the development of the model.

MODEL OF POSTERIOR INTRINSIC MECHANISM

Deficiencies of Transcortical Reflex

Models of cerebral organization relevant to complex psychological processes have been based to a large extent on clinical neurological data and have been formulated with the 'reflex' as prototype. Such models, implicitly or explicitly, assume that the effects of receptor activity are transmitted to receiving or sensory areas; from these, neural activity converges upon the association cortex where 'elaboration' takes place; the 'elaborated' or 'associated' neural events are then relayed to the 'motor' cortex which is considered the final common path for all cerebral activity. These models fail to take into account the finding that extratelencephalic afferents reach the portions of the cortex usually referred to as 'motor' as well as those known to be 'sensory.' Nor do they consider the extent of the origin of efferents from the cerebral mantle, an extent which includes the 'receiving' as well as the 'motor' areas.

Electrophysiological and neuroanatomical experiments demonstrate that somatic afferents are distributed to both sides of the central fissure of primates (1, 38, 66, 82, 126, 152). A recent monograph (74) documents thoroughly the evidence for a more extensive origin of the pyramidal tract from the entire extent of the postcentral as well as from the precentral cortex of primates. This marked afferent-efferent overlap is not limited to the somatic system. With respect to vision, eye movements can be elicited from stimulation of practically all of the striate cortex (145); these eye movements can be elicited after ablation of the other cortical areas from which eye movements are obtained. With respect to audition, ear movements have been elicited from the auditory system (137). From the portion of the cortex implicated in gustation, tongue and chewing movements may be elicited (5, 136); respiratory effects follow stimulation of the olfactory 'receiving' areas (58, 114). Thus, an overlap of afferents and efferents is evident not only in the neural mechanisms related to somatic function but also in those related to the special senses. The overgeneralization to the brain of the law of Bell and Magendie (81) which defines 'sensory' in terms of afferents in the dorsal spinal and 'motor' in terms of efferents in the ventral spinal roots must, therefore, give way to more precise investigation of the differences in internal organization of the afferent-efferent relationship between periphery and cortex in order to explain differences such as those between 'sensory' and 'motor' mechanisms. As yet, only a few experiments toward this end have been undertaken (4, 16, 121).

The afferent-efferent overlap in these projections, or to use a term that takes account of this afferent-efferent overlap, these 'extrinsic' systems, suggests the possibility that the intrinsic systems need not be considered as association centers upon which pathways from the sensory sectors converge to bring together neural events before these can determine movement via the motor pathways. A series of neurobehavioral studies (11, 26, 70, 131, 132, 143), in which the extrinsic sectors were surgically crosshatched, circumsected or isolated by large resections of their surround with little apparent effects on behavior, has cast further doubt on the usefulness of a 'transcortical' reflex model. Additional difficulties are posed by the negative electrophysiological and anatomical findings whenever direct connections are sought between the extrinsic and intrinsic sectors (115, 138). Experimentalists who followed Flourens in dealing with this problem, including Munk (97), von Monakov (139), Goldstein (45), Loeb (79) and Lashley (68), have invariably come to emphasize the importance of the extrinsic sectors not only in 'sensory-motor' behavior but also in the more complex psychological processes. Each investigator has had a slightly different approach

to the functions of the intrinsic sectors, but the viewpoints share the proposition that the intrinsic sectors do not function independently of the extrinsic. The common difficulty has been the conceptualization of this interdependence between intrinsic and extrinsic systems in terms other than the transcortical 'reflex' model—a model which became less cogent with each new experiment.

Partitioning of Sets

There is an alternative concept which meets the objections levied against the transcortical 'reflex' yet accounts for currently available data. The relationship between intrinsic and extrinsic systems can be attributed to convergence of efferents from the two systems at a subcortical locus, rather than to specific afferents from the extrinsic to the intrinsic cortex. Some evidence supporting this notion is already available. Data obtained by Whitlock & Nauta (150), using silver staining techniques, show that both the intrinsic and the extrinsic sectors implicated in vision by neuropsychological experiments are efferently connected with the superior colliculus. On the other hand, lesions of the intrinsic thalamic nuclei fail to interfere with differentiative behavior (13, 102). Thus, the specific effects in behavior of the intrinsic systems are explained on the basis of efferents to a subcortically located neural mechanism that has specific functions. These efferents can be conceived to partition the afferent activity that results in the events in the extrinsic sectors, events initiated by and corresponding to the input variables. Partitioning determines the extent of the range of possibilities to which an element or a set of elements can be assigned. Partitioning results in patterns of information, information given by the elements of the subsets resulting from the partition (140). The posterior intrinsic sector mechanism is thus conceived to provide both referent and units, though not the elements to be specified. The effect of continued intrinsic sector activity will, according to this model, result in a sequence of patterns of information (partitions) of increasing complexity, which in turn allow more and more precise specification of particular elements in the set (or subsets) of events occurring in the extrinsic systems. Thus, through continued posterior intrinsic sector activity, more and more information can be conveyed by any given input. As a result, the organism's differentiative behavior remains invariant under a progressively narrower range of systems of transformation of the input—differentiations become more 'absolute.'

The programing of the activities of the posterior intrinsic sectors remains in question. Some things are clear, however. The advantage of this model is that the program is not composed by the events upon which the program operates. In this respect the model is in accord with neural and neurobehavioral facts (108). Other models, whether associationistic or match-mismatch (6), demand the storage of an ever increasing number of 'bits' of information. The evidence is overwhelmingly against the presence in the nervous system of such minutely specific engrams (71). In the model here presented, engrams consist of encoded programs. These operate on the neural events that are initiated by the input, transforming them into other neural events which can lead to an ever increasingly finer, that is, a more appropriate, differential response (42, 148). In this formulation the posterior intrinsic sectors are conceived as programing mechanisms that function to partition events initiated by the input, not as the loci of association of such events, nor as the loci of storage of an ever increasing number of minutely specific engrams.

NEUROBEHAVIORAL ANALYSIS OF FRONTAL INTRINSIC SYSTEM

The mechanism by which the posterior intrinsic sectors is conceived to affect differential behavior finds a parallel in the mechanism by which the frontal intrinsic sector can affect intentional behavior. The demonstration of this parallel is most effectively initiated by some definitions that allow further analyses of the data obtained in the multiple object discrimination experiment.

Some Definitions

Behavior theory often begins with the statement that a response is a function of certain organismic variables (such as drive or habit) and of a 'stimulus' which is conceived as some environmental event or constellation of environmental events. This classical behaviorist position has been challenged by those primarily interested in psychophysical and perceptual problems (3, 135); these investigators are concerned with the more precise specification of the category 'stimulus' as including 'distal' (e.g. environmental) and 'proximal' (organismic, i.e. receptor) events. This concern must be shared by the neuropsychologist who is interested in the relationship between central processes and behavior since complex interactions

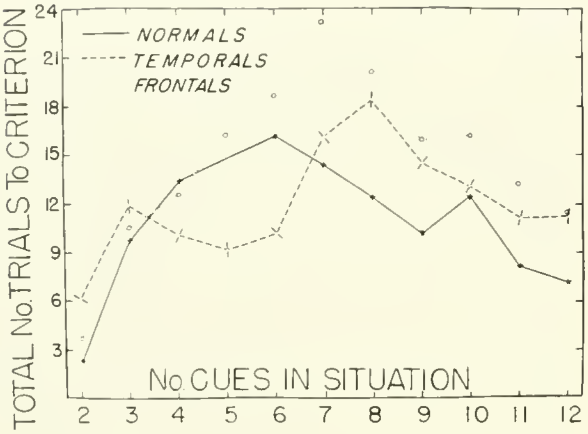


FIG. 10. Graph of the average total number of trials taken in the multiple object experiment by each of the groups (Control = *Normal*; Posterior Intrinsic Lesion = *Temporal*; Frontal Intrinsic Lesion = *Frontal*) to reach, in each of the situations, a criterion of performance of five consecutive correct responses. A correct response occurred when the monkey moved the object under which a peanut had been placed for that trial. In a succession of trials, the peanut remained under one of the objects until criterion performance was reached. Then the peanut was shifted to one of the other objects in the situation and the trials resumed; this procedure was repeated until each of the objects in each of the situations had been the correct one. (See also the legends to figs. 4, 5, and 6.)

between receptor and central mechanisms preclude an understanding of the one without an appreciation of the other. The importance of central regulation of receptor events is attested by the findings of recent physiological experiments which demonstrate mechanisms that allow the regulation of afferent activity through efferents from the central nervous system: the effect of electrical excitation of γ-efferents (one third of the fibers in the ventral spinal root) in modifying the activity of afferents originating in muscle spindles (21, 22, 67); the influence of excitation of efferents in the otic system on afferent activity initiated by auditory stimulation (36); and similar effects in the optic (19, 46), somatic (47, 54) and olfactory (60) systems. (These mechanisms are discussed in detail in Chapter XXXI by Livingston.)

'Stimuli' are thus conceived as centrally regulated receptor events. To avoid confusion, the term 'input' is reserved for those receptor events which can be shown to be systematically related to an ensemble of environmental events. Inputs are specified either by direct observation of the effects of environmental events on receptor events, or indirectly from such effects on the behavioral responses of the organism.

As with the term 'stimulus,' several uses of the term 'response' are also often confounded. As used in this presentation 'response' denotes any dependent variable which is selected as representative of an action, a repertoire of responses which can be shown to be systematically related. Movements of smooth muscle and endocrine events comprise the effector components of action; those components that modify receptor activity (i.e. the stimulus components) are referred to as the 'outcome' of actions. Actions are specified either by direct observations of the outcomes of muscular or endocrine events (e.g. the changes in the activity of afferents from muscle spindles) or indirectly from some behavioral response (e.g. the record of depressions of a lever) made by the organism. The obviously circular relation between all of these definitions is tolerable since each term is independently as well as circularly definable, the environmental terms by physical methods, the organismic terms by biological methods.

Behavior observed to be a function of systematic variations of input is referred to as 'differentiative.' Behavior observed to be a function of systematic variations of outcome is referred to as 'intentional.' Problem solution in all instances involves both differentiative and intentional behavior—however, analysis is profitably focused on each in turn.

Some Experiments

Returning to the multiple object experiment, figure 10 graphs the average of the total number of trials taken by each group of monkeys in each situation to reach the criterion of five consecutive errorless responses. The peculiarities of the shape of the curve representing the performance of the posteriorly operated animals have already been analyzed. The difficulties in performance encountered by the frontally operated group are more clearly demonstrated by comparing the graph of the total number of trials (fig. 10) with one that portrays performance following completion of search, i.e. after the first response in which the peanut is found (fig. 11). Note that the lag shown by the frontally operated group in reducing the number of trials taken to reach criterion (or the number of repetitive errors made) occurs after the peanut has been found (fig. 11). This group of monkeys experiences difficulty in attaining on successive trials the strategy of returning to the object under which on the previous trial they have found the peanut. Whatever may be the explanation of this difficulty, a precise description can be given: for the frontally operated group, 'finding the peanut' does not determine

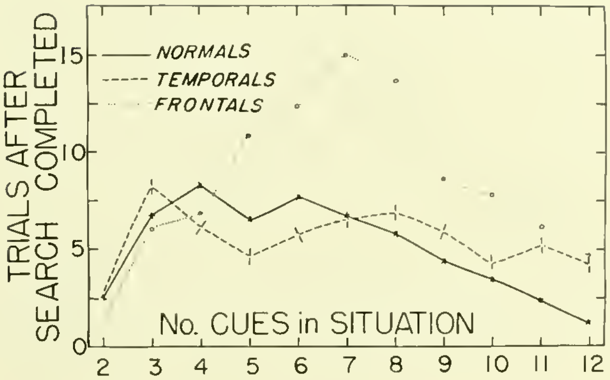


FIG. 11. Graph of the average of the number of trials to criterion taken in the multiple object experiment by each of the groups in each of the situations after search was completed, i.e. after the first correct response. (See legends to figs. 7 and 10.) Note the difference between the curves for the controls and for the frontally operated group, a difference which is significant at the .05 level by an analysis of variance (F = 8.19 for 2 and 6 df), according to McNemar's (85) procedure performed on normalized (by square root transformation) raw scores.

subsequent choices to the extent that 'finding the peanut' determines subsequent choices for the normal group. The experimental behaviorist, using terms identical to those used by Sherrington in his lectures on 'the integrative action of the nervous system,' would describe the finding in more technical language: for the group with frontal lesions, response to the 'positive element,' i.e. the object with the peanut under it, is inadequately 'reinforced' by the finding of the peanut; as a result, the monkeys with frontal lesions do not shift their responses to the reinforced object as readily as do the controls. To state this more generally, when given a choice, the intentions of animals with frontal lesions are guided less than those of controls by the behaviorally relevant consequences, or 'outcomes,' of their prior actions.

Interestingly, before the frontally operated group begins to attain the necessary strategy (after the seven cue situation), performance of this group reflects the number of alternatives in the situation. This finding suggests a parallel with analyses of the determinants of intentions developed in the theory of games and economic behavior (141). Intentions are determined by two classes of variables: *a*) the dispositions of the organism and *b*) an estimate about the actions of other parts of the system. The finding that performance of the frontally operated group is related to the number of alternatives in the situation suggests that this group is deficient in evaluating the second class of variables—but this is only suggested by these results. Support for the hypothesis that frontal lesions do not affect the dispositional variables that determine the preferences comes from the results of another experiment.

In a constant (fixed) interval experiment, 10 rhesus monkeys are tested in an 'operant conditioning' (130) situation which consists of an enclosure (discarded icebox) in which a lever is available to the monkey. Occasionally, immediately after a depression of a lever, a pellet of food also becomes available to the monkey. The experimenter schedules the occasions on which the action of pressing the lever will make a food pellet become available. In this experiment, these occasions recurred regularly at a constant (fixed)

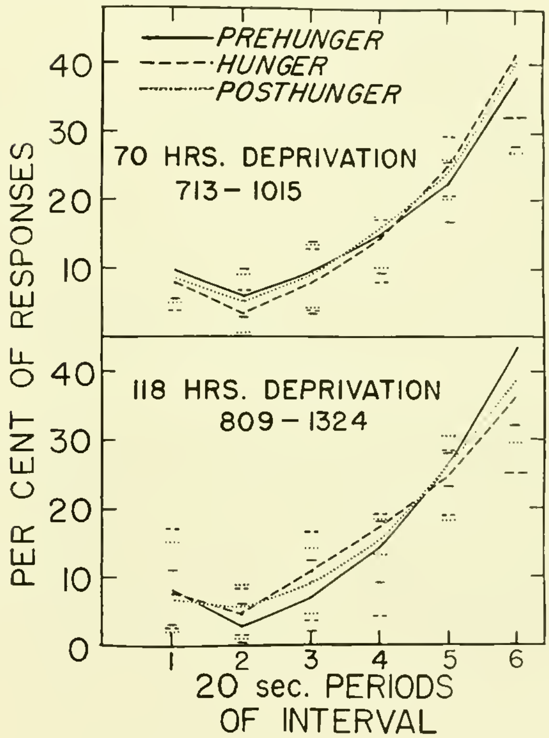


FIG. 12. Graph showing the effect of food deprivation on monkeys' rate of lever-pressing response to food (a small pellet of laboratory chow) which became available every 2 min. The change in total rate is indicated by *numbers* under the deprivation label. The lack of change in the distribution of responses is shown by the *curves*. Each curve represents the average of the responses of 10 monkeys; each point represents the average rate during a period of the interval over 10 hr. of testing. Variance is indicated by the *short horizontal bars*. (Dr. Nathan Azrin made this experiment possible by constructing apparatus and by suggesting that separate counters be used to record performance during each period of the interval. Mr. David Nowel, Mr. Thomas Tighe and Miss Libby Fleisher helped carry out this and the experiment reported in fig. 13.)

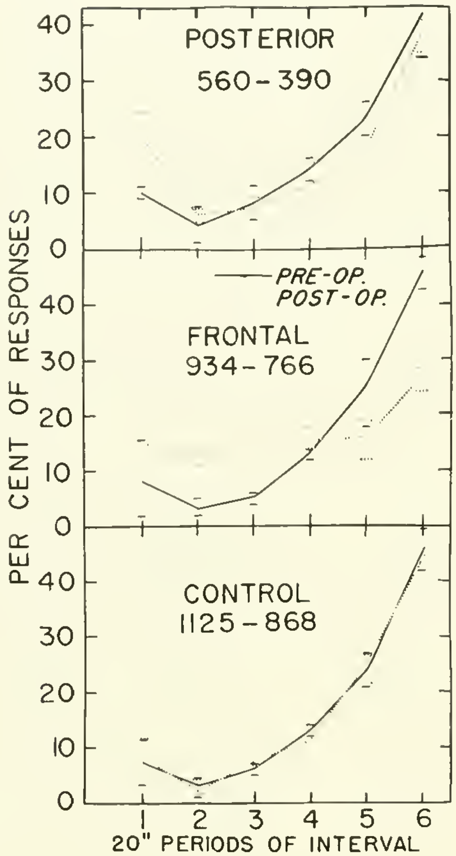


FIG. 13. Graph showing the change in distribution of monkeys' response rate following frontal intrinsic sector ablation (three monkeys). Note that the distribution of rate over the interval is not affected in the controls (four monkeys) and after posterior intrinsic sector ablations (three monkeys). Also note that the total rate of response (*numbers* below names of groups) did not increase; rather that rate was somewhat decreased, probably due to the ad libitum feeding period which all groups were given prior to operation—approximately 2 wk. before postoperative testing. (Compare with fig. 12 and see legend to that figure.)

interval of 2 min. The conditioning procedure as a rule results in performance curves (scallops) which during the early portions of the interval reflect a slow rate of response, and during the latter portions an accelerating rate which nears maximum just prior to the end of the interval. All of the monkeys used in this experiment were trained every other day for 2-hr. sessions until their performance curves remained stable (as determined by superimposition of records and visual inspection) for a least 10 consecutive hours.

Two experimental conditions were then imposed, one at a time: *a*) deprivation of food for 72 and 110 hr., and *b*) resection of frontal and posterior intrinsic cortex. Food deprivation increases the total rate of response of all animals markedly but does not alter the proportion of responses made during portions of the interval (fig. 12). Resection of the frontal intrinsic sector does not change the total number of responses but does alter the distribution of responses through the interval—there is a marked decrease in the difference between the proportion of responses made during the various portions of the interval. Monkeys with lesions of the posterior intrinsic sectors and unoperated controls show no such changes (fig. 13).

Analysis of Results

The results of the constant interval experiment support the contention that the effect of an outcome of an action is influenced by variables which can be classified separately. Deprivation influences total rate of response; frontal lesions, the distribution of that rate. Deprivation variables are akin to those which have in the past been assigned to influence the disposition of the organism. The frontal intrinsic sector lesion appears to influence the monkey's estimate of the situation. This finding is thus in accord with that obtained in the multiple-object problem. Both experimental findings can be formally treated by the device of 'mathematical expectation' (140). The distribution of responses in the constant interval experiment can be considered a function of the temporal 'distance' from the outcome; distribution of response probabilities in the multiple-object experiment is a function of the number of objects in the situation. Frontal intrinsic sector lesions interfere with those aspects of intention that depend on an estimation of the effects that an outcome of an action has in terms of the total set of possible outcomes that are available. The effects of frontal intrinsic sector lesions on behavior related to outcomes thus parallels the effects of posterior intrinsic sector ablations on behavior related to inputs. A general model of intrinsic sector mechanisms seems therefore to be possible. As a step, after a brief review of available data, a model of the frontal intrinsic mechanisms is proposed.

Review of Other Data

The effect of frontal intrinsic sector resection on the distribution of responses in the multiple-object and constant-interval problems is correlated with other deficiencies in preferential behavior that follow such resections. The most clear-cut deficiency is in the per-

formance of delayed reaction and of alternation by subhuman primates. These problems are usually classified with those used primarily to study differentiative behavior, although differences between the two are recognized. These differences have been conceptualized in terms of one-trial learning (99), immediate memory (56) and retroactive inhibition (83), conceptions which are insufficiently distinctive to account for recently reported experimental findings (94). More penetrating analyses have been accomplished for the effects of frontal intrinsic sector lesions on the performance of the double alternation problem (78) and for the simple alternation problem per se (6a). These analyses emphasize the recurrent regularities which constitute the alternation problems and suggest that such problems be considered examples of a larger class which can be distinguished from problems that require differentiation (37). Delayed reaction may also belong to the class of problems specified by recurring regularities; the recurrence, at the time response is permitted, of some of the events present in the predelay situation, constitutes an essential aspect of the delay problem (94).

The reasons for classifying the delayed reaction and alternation problems with those related to systematic variations of outcomes remain somewhat obscure. The results of the following experiment provide some clarification. Under special conditions, monkeys with lesions of the frontal intrinsic sectors perform remarkably well the delayed reaction and alternation problems (93, 94). Adequate performance is established, however, at the cost of a great number of repetitive errors (though not of initial errors), as shown in figure 14. These results can be described as a failure in performance due to the relative inefficacy of the outcome of the frontally operated animals' actions in determining subsequent action. This description is compatible with the finding that, in delayed reaction, the important determinant of performance is the outcome of the animal's reaction in the predelay situation (94), the outcome having 'acquired distinctiveness' during the earlier phases of the experiment.

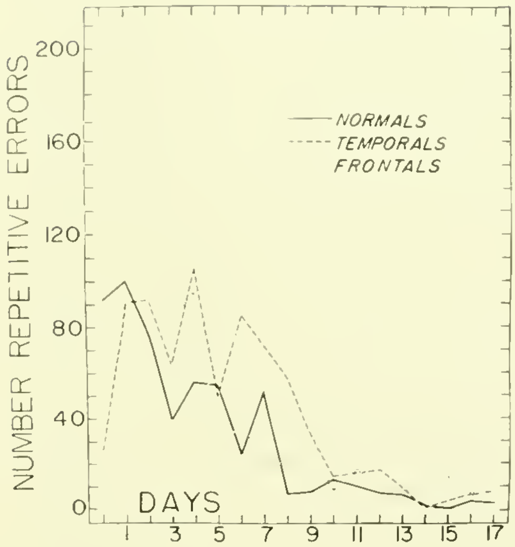


FIG. 14. Graph showing the differences in the number of repetitive errors made by groups of monkeys in a 'go-no-go' type of delayed reaction experiment. Especially during the initial trials, frontally operated animals repeatedly return to the food well after exposure to the 'nonrewarded' predelay cue. Note, however, this variation of the delay problem is mastered easily by the frontally operated group. The 12 rhesus monkeys used in the multiple object experiment (figs. 6 to 11) served as subjects some 2 years earlier in the delayed response experiment portrayed here. (Dr. Margaret Varley assisted in the performance of the earlier experiment.)

MODEL OF FRONTAL INTRINSIC MECHANISM

From these data, a formal model of the neural mechanism that underlies the effect of frontal intrinsic sector resections of intentional behavior can be proposed. This model takes into account the neural relationship between the frontal intrinsic sector and the mediobasal structures of the forebrain (110) and is based on the finding that two classes of variables determine the effects of an outcome of an action. A large body of data has been accumulated in the last 20 years as a result of studies which made use of surgical ablation and electrical stimulation. These data demonstrate the special relation of the mediobasal systems of the forebrain to the class of variables subsumed under the rubric 'disposition.'

Mediobasal Forebrain and Disposition

Changes in the following types of behavior are reported to result from mediobasal forebrain ablations and stimulations: fighting (dominance, reaction to frustration); fleeing (escape and avoidance); feeding (appetitive, such as hoarding, and consummatory); and mating and maternal (nest building and care of the young). Stimulation or ablation which affects one of these behavior patterns is likely also to affect the others (though not necessarily to the same extent). On the other hand, the performance of discrimination tasks remains unaffected (107).

Typically the damage or stimulation of mediobasal sectors affects intentional behavior by disrupting the more or less orderly recurring sequences of actions which constitute feeding, fighting, fleeing, mating and maternal behavior. None of the elements of the sequence drop out; rather the duration of any one such element of action is altered. The outcome of an action appears, in these damaged animals, to be an ineffective terminant or maintainant of acts in the sequence (18). Specifically, animals with mediobasal forebrain resections continue feeding long after control subjects (with the same amount of deprivation and in the same situation) have stopped eating (34, 111). The duration of avoidance behavior is shortened: thus, a monkey will repeatedly grasp a flaming match even though he is burned each time (35). A fighting reaction is not maintained. An animal with a mediobasal lesion may draw blood or have a finger bitten off and within a few seconds sit unconcernedly munching peanuts. This effect, as that on avoidance, is especially easy to discern in measures of extinction (117). Reactions to a 'frustration situation' are also altered along this dimension: the intensity of an animal's reaction to frustration is unimpaired, but the duration of the reaction is shorter than that of a control subject (113). When closely examined, the effects of mediobasal forebrain ablations on hoarding (133), mating (34) and maternal (134) behavior, are on the duration of a particular element of the sequence, for example, food or an infant is dropped before the nest is reached or, occasionally, carried to the nest and then taken out again to be dropped elsewhere.

The neural mechanisms whereby the mediobasal sectors affect the outcome determinants of behavior are only beginning to be detailed (109). Essentially, the mediobasal forebrain structures are especially related afferently and efferently to medial mesencephalic and diencephalic structures in which are located the slowly adapting receptors surrounding the third and fourth cerebral ventricles (such as the osmo- and temperature-sensitive elements) as well as to the nonspecific diffuse systems. The latter are characterized by networks of short fine-fiber neurons. In such networks synaptic, dendritic and electrotonic phenomena, especially sensitive to neurochemical influences, are most likely of greater total significance than are rapidly propagated patterns of neural impulses. In fact, the connections between the mediobasal forebrain and medial mesencephalic and diencephalic structures are so arranged that even when propagated signals are transmitted, the effect on the target site is more often a change in local excitability than the firing of neurons (44).

Characteristic interactions between the functions of the mediobasal sectors and those of the diffuse nonspecific systems are thus clearly established at the neural level—interactions which can account for the finding that intentional behavior is affected when mediobasal forebrain structures are ablated or electrically excited. An analysis of the effects of these interactions can therefore be undertaken. Changes in the excitability of these neural mechanisms have been correlated with changes in activation, such as sleep-wakefulness, which in the intact organism are cyclic processes. Whether the outcome of any particular action is desirable or not is a cyclic function—for instance, a heaping plate of food is most desirable at the peak of the appetitive cycle but slightly nauseating just after consumption of a large meal. The differences in the effects of outcomes depend therefore on the dispositions of the organism that are only partially (and inadequately) described by the differences that can be found to occur during any one cycle (27, 28, 48, 77, 118). More complete description would take into account cyclically recurring regularities.

The cycles of activation (or deactivation) in behavior that occur with changes in the excitability of the central system are analogous to conversions between potential and kinetic energy in physical systems—the activity of water at the base of a fall is not properly described in terms of the differences between the 'amount' of energy which exists in the limpid pool at the top of the falls and that which characterizes the excited turbulence at the base. Rather, the difference is measured by reciprocally related quantities—kinetic and potential, in the case of physical systems (such as the waterfall); or anabolic and catabolic, in biological descriptions. Thus, a 'need-reduction' formulation, in which the referent against which change is specified is considered to be some basal (that is minimal) level is inadequate. This conceptualization, by insistence on 'amount' of need as the basic variable, easily falls into the trap of confusing the reciprocally related potential and kinetic manifestations of the energic process with quantitative differences in the total amount of energy in the system.

An added argument against simple need 'reduction,' based on the notion of 'physiological need,' is that such a notion does violence to physiological fact. Oxygen deprivation produces little increase in respiratory rate, provided a constant partial pressure of carbon dioxide surrounds the respiratory receptor

mechanisms in the carotid body and brain stem (87). Food deprivation, as in starvation, is insufficient per se to increase appetite. Long-term deprivation of mating leads as often to continence as to frustration—these examples suffice to suggest that physiological need is not invariably produced by deprivation. And, of course, the converse also holds, in that 'need' (as measured by the rate or amount of movement related to an outcome) may actually increase when recurrently 'satisfied' (77).

On the other hand, the more complete specification that takes into account the reciprocally related recurring changes in the distribution of excitability and rest is supported by physiological fact. The electrical activity of totally isolated neural tissue is cyclical (7). The period of cyclical activity can be specified and any changes imposed on the normal periodicity can be described. The advantages of such description are: the 'amount of excitability' is not confused with 'amount of energy'; a particular event may increase excitability at one time, and may decrease it at another; thus, the effect of an outcome of an action is conceived to depend on the phase of the excitability cycle at the moment of action. The disposition of an organism is therefore a basic determinant of intentional behavior. Dispositions are conceived to be dependent on changes in the periods of neural excitability cycles.

Mechanism of Expectation

By analogy with the model describing the functions of the extrinsic and posterior intrinsic mechanisms, the proposal of a model of the frontal intrinsic and mediobasal forebrain mechanisms begins with a statement of the variety of transformations of descriptions of the outcome under which behavior remains invariant. Following extensive bilateral resections of the mediobasal systems, behavior remains invariant over a wide variety of transformations of outcome, for example, even gross changes in the amount of food deprivation minimally alter rate of response to food (147).

Frontal intrinsic sector lesions affect intentional behavior that remains invariant only under the more restricted ranges of transformations of the outcome, transformations which in controls can be shown to affect the distribution of intentional responses. In the extreme, unique distributions, such as those measured by indifference functions, would be most affected by such lesions.

Unique distributions can occur only when both the units of intention and their referent have been fixed. Difficulties in defining such units and their referent stem from the cyclical variations which describe the dispositions of organisms—difficulties already discussed from the neurobehavioral standpoint. The formal device 'mathematical expectation,' which is so usefully applied to the analysis of the effects of frontal intrinsic sector lesions, is designed to overcome the difficulties encountered in analyzing the solution of problems characterized by cyclic phenomena (141). This device, based on combinatorial (equilibratory) and set theoretical methods, meets the difficulties by the suggestion that the solution of such problems is described, not by the single elements (outcomes) that define the problem, but by sets (and subsets) of such elements. Unfortunately, the mathematics falls somewhat short of accomplishment in this area and only some rudimentary approaches to the task are possible at this time (142).

Nevertheless, the relevance of the device, mathematical expectation, in the analysis of the results of the multiple-object and constant-interval experiments, suggests the formal model of the frontal intrinsic mechanism. This model conceives the frontal intrinsic mechanism to partition the events in the mediobasal forebrain systems, dispositional events that determine the effect of outcome variables. Partitioning results in distributions of intentions, intentions determined by the elements of the subset resulting from the partition. The frontal intrinsic mechanism is thus conceived to provide both referent and units although not the elements that specify intentional behavior. The effect of continued frontal intrinsic sector activity will, according to this model, result in an increasingly complex sequence of distributions of intentions which in turn allow more and more precise specifications of intent that can be conveyed for any given outcome. As a result, the organism's intentional behavior remains invariant under a progressively narrower range of systems of transformations of outcomes—intentions become more precise.

The programing of the activities of the frontal intrinsic sector remains in question. Some things are clear, however. The advantage of the model is that the program is not composed by the events upon which the program operates. Thus, as in the case of the posterior intrinsic mechanisms, storage of encoded programs is demanded—not storage of an ever-increasing number of discrete preferences. In this formulation, the frontal intrinsic sector is conceived as a programing mechanism that maps intentions—a conception that is in accord both with experimental

finding and clinical observation (23, 32, 101, 103, 127).

SUMMARY AND CONCLUSION

Evidence has been presented to support the conception that the posterior and the frontal intrinsic systems serve different aspects of the problem-solving process. The argument has been forwarded that two major classes of behavior can be distinguished, differentiative and intentional. The multiple object experiment detailed above provides a paradigm of the relation between each of these classes in problem solution. Posterior intrinsic sector resection interferes with differentiative behavior during search; such lesions affect the delineation of a problem. Frontal intrinsic sector resection interferes with intentional behavior after search is completed; such lesions affect the economic solution of a problem.

Furthermore, the experiment presented shows that the delineation and economic solution of a problem can occur more or less haphazardly. Haphazard problem-solving behavior is described by the relatively wide range of systems of transformations of the input and outcome under which behavior remains invariant. Strategic problem solution, on the other hand, occurs with restriction of the range of such systems of transformations. The experiment is interpreted to indicate that restriction in this instance results from the operation of a mechanism (the intrinsic) that partitions the neural events (in the extrinsic and mediobasal forebrain systems) determined by input and outcome. By providing both a referent and units, partitioning defines the range of possibilities to which an input or outcome is assigned by the organism.

The distinction between neural mechanisms that serve differentiation and those that subserve intention is not a new one. Sherrington makes this distinction in his description of the coordination of reflexes (129): The "singleness of action from moment is the keystone in the construction of the individual." This singleness of action comes about in two ways—'interference' between and 'allied combinations' of reflexes. In his analysis of 'interference' (or antagonism) between reflexes, Sherrington forwards concepts such as inhibition, induction and spinal contrast—concepts which have relevance to discriminative behavior [for example, as already noted, the use of the concept 'induction' by Skinner (130) for the occurrence of the 'hump' in the graphical representation of complex discrimination learning]. Sherrington uses these concepts to provide an understanding of the differences between reflex behaviors to different inputs. On the other hand, Sherrington's discussions of 'allied combinations' of reflexes are an attempt to understand behavior regulated by outcomes: "the new reflex breaks in upon a condition of equilibrium, which latter is itself a reflex," a notion which has been enlarged upon by Cannon (9) and more recently by Wiener (151). In discussing allied combinations of reflexes, concepts such as reinforcement, convergence, summation and facilitation are used by Sherrington—concepts which have relevance to intentional behavior.

More recently, Denny-Brown (17) has distinguished between cortical resections that affect patterns of approaching (grasping, hopping, placing) and those that affect patterns of avoiding (withdrawing). Although the cortical resections made by Denny-Brown and those described here are only roughly comparable, enough correspondence exists to permit the suggestion that the patterns of approaching and the sampling of inputs as described here may reflect some common mechanism, that the patterns of avoiding may be manifestations (in untamed animals subjected to laboratory routines) of the behavior described here as guided by outcomes.

The neural mechanism here proposed is similar in some respects to others already formulated. The neurobehavioral data presented, and their formal analysis, suggest that the events in the extrinsic and mediobasal forebrain systems are indeed the important determinants of moment-to-moment behavior as in Lashley's (72) and in Köhler's formulations (63–65), among others. However, these events are acted upon by others which provide the contextual matrix that sets limits on the moment-to-moment behavior, as proposed by Freud (33) and more recently by Forgus (29–31). The resultant of the interaction of these two classes of neural events is described more formally, though less picturesquely, by the mechanism, 'partitioning of sets,' than this resultant is described by Lashley's largely nativistic or Hebb's largely empiricistic conceptions: reduplicated neural loops (69) or phase sequences (53). Yet all three share the essential characteristic that, in continued problem-solving behavior, increasingly complex patterns of neural events occur, patterns that allow more and more precise differentiations and intentions to be made.

Nor is the distinction between the delineative and the economic aspects of problem solution a new one in the behavioral sciences. The contributions of the

Würzburg school (55) and their Gestalt-oriented successors (2, 62, 149) have consistently emphasized the distinction between the 'content' of thought and its 'motor'; between knowledge and intention (62). These formulations, however, frequently confounded two of the pairs of distinctions made in this presentation: the distinction between the delineative and the economic aspects of problem solution on the one hand and, on the other, that between the attitudinal (partitioning) factors and the events upon which these attitudes operate. Piaget (104) comes somewhat closer to maintaining separate these distinctions. This correspondence between Piaget's analysis of the results of his experiments and that presented here may be due to the similarity of the formal devices used: Piaget's 'groups of displacements' are included in the 'systems of transformations' referred to throughout this presentation.

Social scientists have also made use of the distinction between the delineative and the economic aspects of problem solution. Thus, Parsons distinguishes between determinants of 'interest' in a problem and those of 'value-orientation which provide the standards of what constitute satisfactory solutions of these problems' (100). Basic to this distinction is the difference as yet grasped only vaguely, between the acquisition of information (128) and its utilization (140–142). The development of this distinction in the social, as well as in the biological (and in the physical) sciences, is hampered by the fact (already mentioned above) that, in connotative use, the language of occidental cultures fails to separate clearly the differences brought out by the neurobehavioral analysis made here: differences between attitudinal factors and the events upon which these attitudes operate on the one hand, and between the delineative and the economic aspects of problem solution on the other. Recently, there has been in North America a shift in popular connotation away from attitudinal determinants—e.g. the term 'honesty' no longer refers exclusively to 'telling the truth,' 'respecting others' property' and such, but also to 'behaving according to how one *feels* and *sees* the situation,' even if this entails occasional lying or stealing (119). Such confusion in connotative meaning creates especial difficulties for a science that must obtain data almost exclusively from verbal reports. The results of analyses such as this one of neurobehavioral data may be most usefully applied to the social sciences as keys that open avenues of conceptualization common to all sciences—conceptualizations now locked behind the intricacies of verbal behavior.

> We thus, from the biological standpoint, see the cerebrum and especially the cerebral cortex, as the latest and highest expression of a nervous mechanism which may be described as the *organ of, and for, the adaptation of nervous reactions.* The cerebrum, built upon the distance-receptors and entrusted with reactions which fall in an anticipatory interval so as to be *precurrent* . . . , comes, with its projicience of sensation and the psychical powers unfolded from that germ of advantage, to be the organ *par excellence* for the readjustment and the perfecting of the nervous reactions of the animal as a whole, so as to improve and extend their suitability to, and advantage over, the environment. . . . Only by continual modification of its ancestral powers to suit the present can it fulfil that which its destiny, if it is to succeed, requires from it as its life's purpose, namely, the extension of its dominance over its environment. For this conquest its cerebrum is its best weapon. It is then around the cerebrum, its physiological and psychological attributes, that the main interest of biology must ultimately turn.
>
> Sherrington, C. S. *The Integrative Action of the Nervous System*, p. 390 (129).

Whatever the merit of this manuscript, much is due to George Miller who led me by the hand through the formidably formal gardens of mathematics and who instigated not only the experiment but also many of the ideas reported; to Jerome Bruner who initially posed a number of the psychological problems discussed here and who gave encouragement through the difficulties of solution; to the several others who at one time or another provided ideas and support to the effort: Jane Connors, Eugene Galanter, Edward Green, Hellmuth Kaiser, Harriet Knapp, Judy and Walter Rosenblith; to W. S. Battersby and Ernest R. Hilgard for their helpful comments on earlier drafts of this attempt; to Jerome Schwartzbaum for valuable help with statistical problems; and to the 12 little rhesus monkeys who skillfully, patiently and impatiently played the multiple object game with me daily for 6 months. The experiments described were performed as part of a program of research generously supported by grants from the National Institutes of Health, Department of Health, Education and Welfare, and from the Division of Psychiatry, Department of the Army.

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Cingulate, posterior orbital, anterior insular and temporal pole cortex

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CHAPTER CONTENTS

INTRODUCTION

CONSIDERABLE INTEREST IN THE cortical areas discussed in this chapter has been provoked by the suggestion that they serve autonomic and emotional rather than olfactory functions. The possible role of these regions in the effects obtained in the surgical treatment of psychiatric disorders by interference with frontal and anterior temporal structures and the frequent occurrence of epileptogenic discharges in the anterior temporal region have provided a remarkable impetus for clinical and neurophysiological investigation of this portion of the brain. Reviews of these studies have been written by Fulton (74–76), MacLean (162–164), Kaada (126, 127), Gastaut (83), Dell (55), Klüver (140), Pool (197), Pribram & Kruger (202) and Gloor (92).

SOME GENERAL ANATOMICAL CONSIDERATIONS

On the medial surface of the cerebral hemisphere, the rostral brain stem and the interhemispheric commissures are surrounded by a great arcuate convolution, the dorsal and ventral halves of which are the cingulate (limbic) and hippocampal gyri (figs. 1, 2). The former surmounts the corpus callosum and can, in most mammals, be traced beneath the genu of the corpus callosum as the subcallosal gyrus to the olfactory tubercle. In primates the cingulate and hippocampal gyri are clearly demarcated by the cingulate sulcus and the rhinal fissure respectively.

Varying terminology has been applied to this part of the brain. In agreement with the approved international anatomical nomenclature (57, 243) and with most recent authors, the term cingulate gyrus is here preferred for the dorsal half of the arch. This has also been spoken of as the limbic (22, 209, 260, 261) or fornicate gyrus (34, 35). Finally the entire two

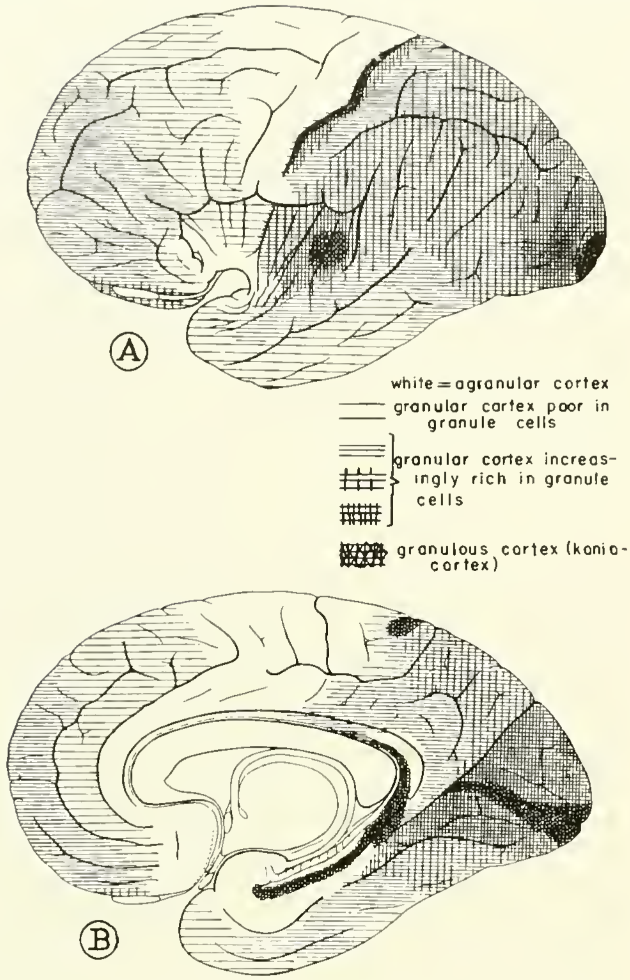

FIG. 1. Distribution of agranular (*white*) and different types of granular and granulous cortex in man, according to von Economo. [From von Economo (261).]

arcuate convolutions, taken together, were earlier designated the cingulate (261) or fornicate gyrus (205, 206), the limbic lobe (249) or the *grand lobe limbique* (34, 35). The latter term also includes other structures (cf. below).

Posteriorly the two gyri are continuous in the retrosplenial region. Anteriorly the cortex of the posterior orbital surface of the frontal lobe, the anterior insula and adjacent temporal pole is interposed between the anteroventral ends of the two convolutions, thus completing a cortical ring around the rostral brain stem and interhemispheric commissures. Closely associated with these convolutions is the hippocampus proper. Based on phylogenetic studies Herrick (100) made a distinction between 'archipallium' (hippocampus, fascia dentata and subiculum), 'paleopallium' (pyriform cortex covering the anterior portion of the hippocampal gyrus) and 'neopallium.' The archi- and paleopallium are covered by an ancient type of cortex termed allocortex (259). The grey matter of the rest of the ring-like formation forms a 'transitional' cortex, also termed 'juxtallocortex,' which separates the typical allo- and isocortex. Part of this juxtallocortex has also been designated 'mesocortex' (for references cf. 126, pp. 72–86; 202).

The general concept of most morphologists has been that all these allo- and juxtallocortical structures are concerned with important olfactory functions and they formed the basis for Broca's (34) delimitation of his *grand lobe limbique*. The anterior part of the cingulate gyrus was specially designated as *le centre olfactif supérieur*. All these structures have also been variously included in the ill-defined terms 'rhinencephalon' or 'olfactory brain.' Subsequent anatomical and physiological research has not given any support to the presumed olfactory function of the cingulate region, the hippocampus and some other parts of the 'limbic lobe' (see 36, 126, 162, 184, for review and references).

More recently Broca's term 'limbic lobe' has been adopted by MacLean and others (162, 163, 166). The cortex of the posterior orbital surface of the frontal lobe, the anterior insula and the temporal polar region which, by Broca's definition, would be outside the 'limbic lobe' (because it is peripheral to the rhinal fissure) has, on account of its close cytoarchitectural (260, 261) and functional (126, 133) similarities to the adjacent allo- and juxtallocortex, also been included. At our present state of knowledge the term 'limbic lobe' is, in the reviewers opinion, of doubtful value, even though it is convenient. The same applies to the still broader term 'limbic system' (10, 76, 164, 166) which, in addition to the cingulate and hippocampal gyri, the hippocampus, and the orbitoinsulotemporal polar region, includes all the subcortical cell stations presumably associated with the 'limbic lobe' (amygdala, septal nuclei, hypothalamus, epithalamus, anterior thalamic nuclei, and parts of the basal ganglia) (163, 166). Although the cortical areas contained in the 'limbic lobe' may share some structural characteristics, it is not known whether they form a functional unit. Recent anatomical and physiological research rather tends to fractionate the 'limbic system' into several units with quite different projections and functional significance. We shall return to this important question at the end of this chapter.

The areas to be dealt with in this section, viz the anterior cingulate, posterior orbital, anterior insular

and temporal polar regions represent the anterior half of the allo- and juxtallocortical hilar formation. Physiological experiments, particularly in the past 10 years, have shown that these areas respond to electrical stimulation with a great variety of somatomotor and visceromotor effects, thus imputing to it motor functions. This view is consistent with the histological findings that the responsive ancient type of cortex is of the agranular or sparsely granular type which, therefore, might be expected to possess effector functions (fig. 1).

On the other hand, this ancient type of agranular 'motor' cortex on the medial and basal aspects of the cerebral mantle may also be regarded as interposed between the upper and lower ends of the precentral motor cortex of the dorsolateral aspects of the hemisphere, joining the latter at the cingulate sulcus on the one side and at the lower precentral and anterior insular region on the other (fig. 1). Thus, the physiological experiments lend support to von Economo's (261) contention of the existence of a broad zone of 'motor' cortex which encircles the entire cerebral hemisphere in a frontal plane anterior to the central sulcus of primates.

The limited space at disposal unfortunately does not allow any anatomical description of the cortical areas concerned. The reader is referred to the following more recent publications: cytoarchitecture (reviews: 126, 202; cingulate cortex: 22, 205, 209, 238, 260; orbitoinsular cortex: 22, 29, 73, 260; and temporal polar cortex: 22, 260); corticocortical connections (cingulate: 23, 167, 203, 204, 228; orbitoinsulotemporal cortex: 24, 167, 192, 203, 204); afferent and efferent subcortical projections (reviews: 46, 75, 92, 126, 202; cingulate: 46, 47, 91, 194, 201, 228; orbitoinsular: 46, 200, 215, 256, 264, 268; and temporal polar cortex: 4, 39, 195, 200, 224, 244, 263); and olfactory pathways (2, 36, 37, 176, 202, 205). The subcortical pathways mediating the different types of responses obtained on stimulation are discussed in the subsequent sections.

At this point brief mention should be made of the hippocampal-cingulate relationships. Two distinct types of cortex can be distinguished in all mammals within the cingulate gyrus: a posterior granular type and an anteriorly situated agranular type. The cingulate cortex is closely connected with the hippocampus through the fornix via the mammillary bodies through the anterior thalamic nucleus to the cingulate gyrus. The thalamocingulate projections are derived from all three portions of this nucleus: the anteromedial nucleus, projecting upon the agranular anterior cingulate area (Brodmann's area 24); the anteroventral nucleus, projecting upon the granular posterior cingulate area (area 23); and the anterodorsal nucleus, projecting upon the retrosplenial region (areas 29 and 30). [Reviews and references may be found in various publications (22, 46, 126, 209, 260).] In all these cortical areas (and in the granular prefrontal cortex) (3) the fibers of the cingulum bundle originate and run through the white matter in the retrosplenial region to terminate mainly in the subiculum and presubiculum (1, 3, 80, 205) and possibly directly in the hippocampus proper (205, 228). Thus the cingulum fibers appear to complete some kind of a 'circuit' between the cingulate cortex and the hippocampus, as first suggested by Papez (184) in 1937 in his much publicized theory on the central mechanism of emotion.

Along the sulcus cinguli bordering areas 24 and 23, there is the so-called 'cingular belt,' homologous with areas 32 and 31, which Bailey *et al.* (23) in 1944 found to receive connections from the cortical 'supressor' areas (24s, 8s, 4s, 2s and 19s). Le Gros Clark & Meyer (46) have referred to this belt "as a nodal point of considerable physiological activity," but to the author's knowledge there are no experimental or clinical data that give any clue as to its functional significance and it will therefore not be dealt with any further in this review.

EFFECTS OF STIMULATION

Electrical stimulation of the anterior cingulate and orbitoinsulotemporal polar cortex has elicited complex somatomotor, autonomic, behavioral and electrocorticographic effects which will be described in this order. The effects on respiratory movements will be discussed together with the somatomotor responses as they are subserved by somatomotor nerves innervating striated muscles.

Somatomotor Responses

INHIBITION OF RESPIRATORY MOVEMENTS. One of the more striking effects of stimulation of anterior cingulate cortex on the medial surface and the orbitoinsulotemporal polar cortex on the ventral surface of the hemisphere is the profound inhibition of respiratory movements. This effect is part of a more generalized inhibitory influence on spontaneous somatomotor movements exerted by the same cortical areas.

Slowing or arrest of respiratory movements was

early obtained from the orbital gyrus of cats and dogs (51, 199, 241, 257) and by Spencer (241) from the posterior orbital surface of the frontal lobe of the monkey. These papers were, however, largely forgotten until the report of Bailey & Sweet in 1940 (21) who substantiated and extended the earlier observations in cats and monkeys. In the past 15 years the orbital surface has been extensively studied in the cat (21, 108, 126, 215, 234, 240), dog (54, 126, 215, 234, 240), monkey (54, 126, 133, 159, 215, 256) and man (41, 42, 158). Of particular importance was the observation by Sugar *et al.* in 1948 (245) that in monkeys the posterior orbital respiratory area continues into the anterior insula. The next year Kaada and co-workers (133) reported similar effects in the monkey on stimulating the temporal polar cortex, a

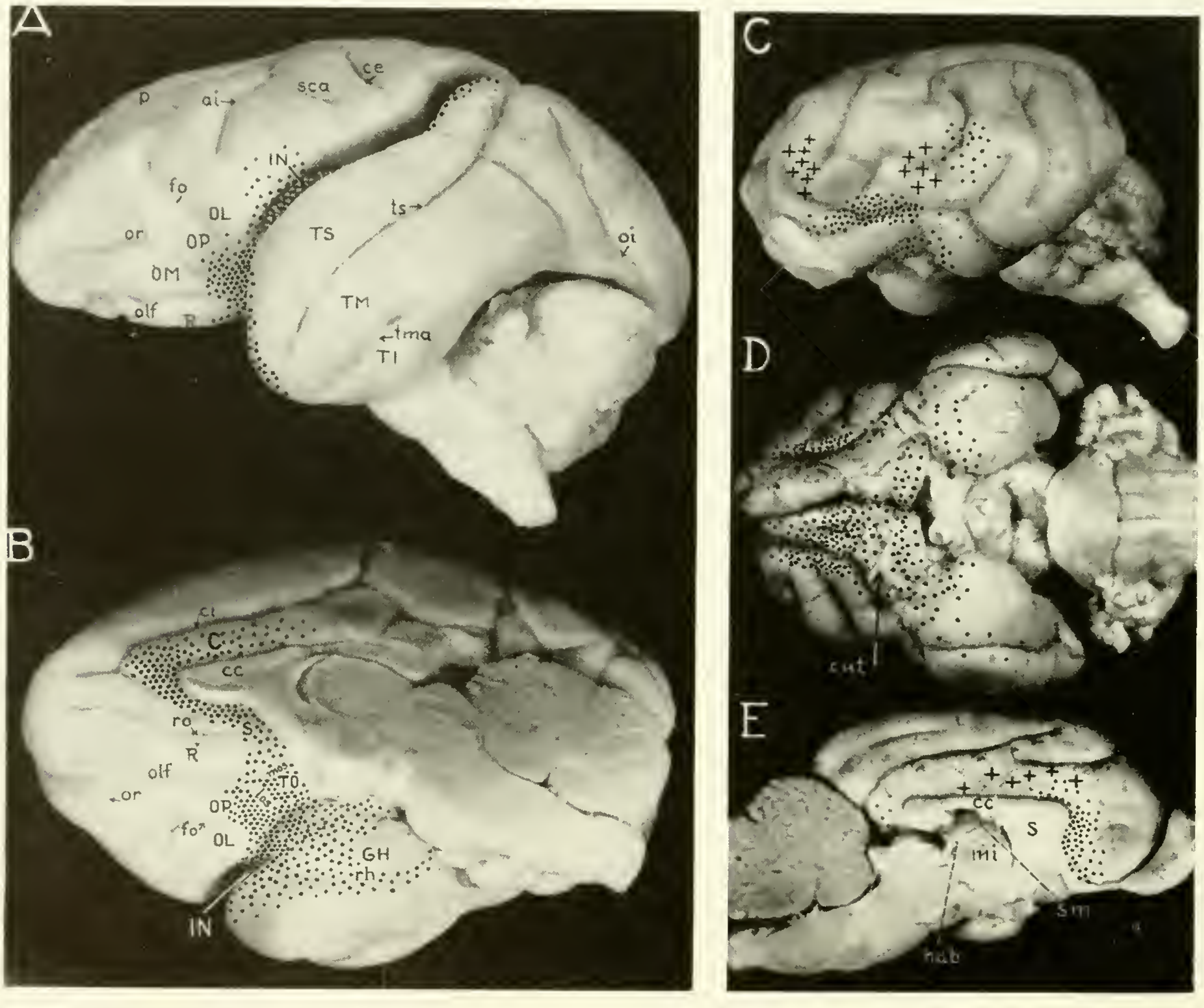

FIG. 2. Anteroventrolateral (*A*) and ventromedial (*B*) view of the hemisphere of *Macaca mulatta*. Insula partly visualized by separation of the temporal and frontoparietal opercula. Area yielding inhibition of respiratory movements with arrest in expiration indicated by *dots*. *ai*, inferior ramus of the arcuate sulcus; *C*, cingulate (limbic) gyrus; *cc*, corpus callosum; *ce*, central fissure; *ci*, cingulate sulcus; *fo*, fronto-orbital sulcus; *GH*, hippocampal gyrus; *IN*, insula; *los* and *mos*, lateral and medial olfactory striae; *OL*, lateral orbital gyrus; *olf*, olfactory tract; *OP*, posterior orbital gyrus; *or*, orbital sulcus; *R*, gyrus rectus; *rh*, rhinal fissure; *ro*, rostral sulcus; *S*, subcallosal gyrus; *TO*, olfactory tubercle. (*C*) Anteroventrolateral, (*D*) ventral and (*E*) medial view of cat brain. Areas yielding inhibition (*dots*) and acceleration (+) of respiratory movements. In (*D*) the right olfactory bulb and tract have been removed in order to visualize the underlying responsive cortex, chiefly the ventral aspect of the gyrus proreus. *cc*, corpus callosum; *hab*, habenula; *mi*, massa intermedia; *S*, septum pellucidum, *sm*, stria medullaris. [From Kaada (126).]

region which was found to be continuous with the responsive orbitoinsular field. A more detailed study of these respiratory inhibitory zones has appeared (126). The existence of an inhibitory insular (115, 132, 263) and temporal polar (10, 93, 115, 156, 195, 263) field in monkey and man has been confirmed.

In 1945 Smith (238) first reported the respiratory inhibitory effect exerted by the anterior cingulate cortex in the monkey. Tower (254), working with lightly etherized cats, had previously included this region in her frontal inhibitory field which also comprised the entire gyrus proreus. The response from the anterior cingulate has later been studied in the cat (10, 59, 107, 113, 126, 240), dog (44, 126, 147, 240), monkey (126, 133, 227, 266) and man (132, 156, 198).

Monkey. In the monkey the inhibitory area on the medial surface appears to correspond closely to the agranular anterior cingulate region (fig. 2*B*). The responsive field extends through the subcallosal region towards the ventromedial edge of the frontal lobe where it seems to be continuous with the respiratory inhibitory area of the posterior orbital surface of the frontal lobe (126, 133). There is an area with optimal effects in the region surrounding the genu of the corpus callosum (126).

On the ventral surface the respiratory inhibitory area (fig. 2*B*) includes the olfactory tubercle and approximately the posterior one fourth of the cortex of the gyrus rectus and the medial, posterior and lateral orbital gyri. The most sensitive zone is the olfactory tubercle and the posterior orbital gyrus rostral to the lateral olfactory stria (area 13) (126, 215). This low-threshold area continues without interruption into the anterior insula (fig. 2*A*, *B*) (115, 126, 133, 245, 263) with the most pronounced effects from the limen insulae. Via the 'buried' anterior upper bank of the sylvian fissure, the responsive anterior insular area extends (with a higher threshold) onto the lateral surface of the frontal lobe and includes a small portion of the lower end of the precentral region (126). This portion represents the area (6B) from which several earlier investigators, stimulating the dorsolateral frontal surface only, had noted respiratory inhibition in the monkey (234, 259, 262), chimpanzee (262) and man (38).

In the temporal lobe of the monkey the region yielding respiratory inhibition (fig. 2) continues unbroken from the anterior insula onto the anterior end of the hippocampal gyrus (uncal region) and the neighboring cortex of the temporal pole lateral to the rhinal fissure (area 38 or TG in von Bonin and Bailey's terminology) (115, 126, 133). Weak responses in lightly anesthetized animals have also been obtained from a narrow strip extending backward along the rhinal fissure on the ventral surface towards and into the retrosplenial region (126). This is likely the same area from which Showers & Crosby (227) recently obtained respiratory inhibition. The best and most consistent effects result from stimulation of the medial and ventral aspects of the temporal tip (126, 263). According to Poirier & Schulmann (195) the low-threshold respiratory inhibitory area of the medial temporal tip extends farther backward along the hippocampal gyrus and occupies about the medial third of this gyrus at its caudal extremity. Cytoarchitecturally this latter area approximately corresponds to the TH field as mapped by von Bonin & Bailey (260). No effects have been obtained from the dentate gyrus (195) or hippocampus proper (126, 195, 263).

A much weaker but distinct respiratory inhibitory field, separated from the responsive insular and temporal polar areas, has been located in the middle and posterior portion of the superior temporal convolution in lightly anesthetized monkeys (fig. 2*A*) (126). The area extends into the 'buried' cortex of the lower bank of the sylvian fissure.

Respiratory inhibition has also been recorded by stimulating the uncus through implanted electrodes in the conscious monkey (166) and from the orbito-insulotemporal polar region in a conscious infant chimpanzee (126).

The inhibition obtained from all cortical regions outlined above mainly concerns the active phase of the respiratory cycle, i.e. inspiration, with the chest assuming an expiratory position during the period of apnea (fig. 3). The effect occurs almost instantaneously. The respiratory movements cannot be held in abeyance for more than 25 to 35 sec. despite continuous stimulation, after which period respiratory 'escape' occurs. Variations in the stimulus parameters do not alter the character of the response. No frequency-conditioned reversal of the respiratory effects has been produced from these areas in monkeys (126). Optimum inhibitory effect is obtained with frequencies of 40 to 60 cps and prolonged pulse durations of 10 to 20 msec. (126).

Cat and dog. As in the monkeys the optimal inhibitory zone on the medial surface is found just in front of and below the genu of the corpus callosum (fig. 2*E*) (107, 113, 126, 240). Weaker effects only are evoked from the rest of the anterior cingulate and subcallosal (infralimbic) cortex as depicted by Rose & Woolsey (fig. 7*E*) (126). The failure of some inves-

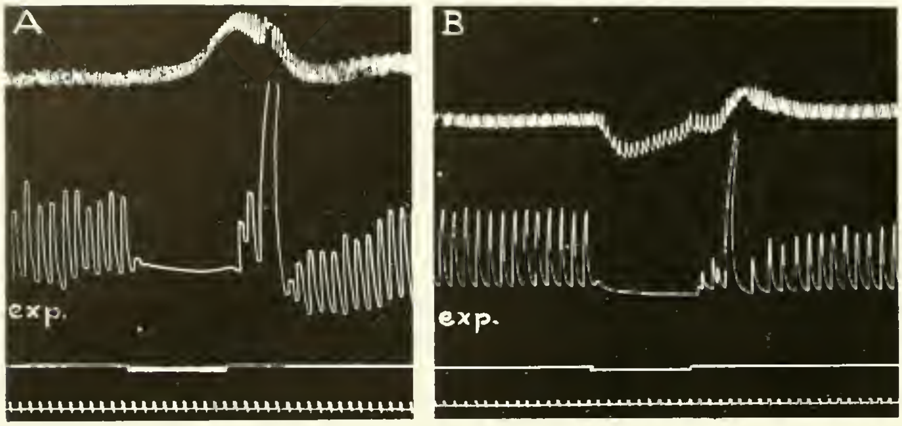

FIG. 3. Inhibition of respiratory movements (*second line*) and arterial pressure alterations (*first line*) following excitation of the anterior cingulate cortex in the monkey. Note opposite arterial pressure effects in *A* and *B*. Ether anesthesia. Time in seconds. [From Smith (238).]

tigators to obtain respiratory inhibition from several points in the anterior cingulate area is probably due to the limited extent of the optimal zone within this area, a point which has not been seriously considered. The effect has also been obtained in unanesthetized dogs and cats by stimulation through implanted electrodes (10, 44, 107, 126).

The basal respiratory inhibitory fields in cats and dogs occupy part of the orbital gyrus (fig. 2*C*, *D*) (21, 51, 54, 108, 126, 199, 215, 234, 240, 241, 257) and also include the olfactory tubercle (126), the anterior portion of the pyriform cortex and the ventral surface of the proreate gyrus which is largely covered by the olfactory bulb and tract (126). Posteriorly the border is indistinct and extends into the rostral ends of the anterior ectosylvian and sylvian gyri. Less intense and fickle responses have also been obtained backward along the rhinal fissure onto the tentorial surface of the hemisphere and into the retrosplenial region (126, 254). As long as the basal respiratory inhibitory field in the monkey was thought to be restricted to the posterior orbital gyrus (the insula and temporal lobe has not yet been studied), the orbital gyrus of cats and dogs was reasonably considered the homologue of this gyrus of primates (21, 54, 215). However, the demonstration in the monkey of an uninterrupted orbito-insulotemporal polar inhibitory field makes it extremely likely that the responsive cortex of the orbital surface of cats and dogs corresponds to the orbito-insulotemporal polar field of primates (126, p. 84).

A separate, less active respiratory inhibitory field (apparently the homologue of that found in the superior temporal gyrus in the monkey) is located in the anterior sylvian and ectosylvian gyri (fig. 2*C*) (126, 254). Complete arrest has only rarely been obtained from this area, the usual response being a slowing of the respiratory rate.

The usual type of inhibitory response in cats and dogs to stimulation of all these areas is similar to that in monkeys, i.e. arrest in expiration. In the author's experience it is not possible in these species to obtain the prolonged and dramatic inhibition observed in the monkey; escape usually occurs after only 10 to 20 sec., even with strong stimulation (126, 240). The optimum stimulus parameters are approximately the same as in the monkey, i.e. a frequency of 40 to 60 cps and prolonged pulse durations of 6 to 10 msec. (126, 240). Far more common than in monkeys is a slowing of the rate without much change in amplitude, or a combination of slowing and decreased amplitude (107, 126). Further, stimulation, particularly of the orbital gyrus of the cat and dog, frequently results in arrest in inspiration irrespective of whether the stimulus is applied during the inspiratory or expiratory phase (126, 241). Also on central vagal stimulation such 'inspiratory effects' are weaker in monkeys than in dogs, cats and rabbits (276). This feature therefore possibly denotes a species difference.

The cortical origin of the respiratory effects from the various parts of the medial and basal zones in the monkey, cat and dog has been demonstrated (126). The effects are not due to spread of current to the dura, blood vessels, cranial nerves or to subcortical structures (126). Further, the response from a given area is not initiated by activation of other cortical areas through corticocortical connections. Thus, for instance, the effects obtained from the orbital surface and from the temporal pole in the monkey remain unaltered after section of the uncinate fasciculus (126, 133) which is known to connect the two areas reciprocally (192, 203). The influence is mediated directly 'downstream' by corticosubcortical fibers, outside the pyramidal tract and the hippocampus-fornix system (126). The possible subcortical routes are discussed below.

Man. In man arrest of breathing quite similar to

that recorded in animals has been obtained on stimulating points in the same regions as those outlined above for the monkey, cat and dog. The responses have been produced in patients under light pentothal anesthesia from the anterior cingulate (132, 156, 198, 273) and posterior orbital surface (41, 42, 158) as well as in the conscious patient from the same areas and from the anterior insula (132) and the ventromedial aspect of the temporal pole, particularly in the region of the uncus (93, 132, 156). Stimulation of the lateral surface of the temporal pole in man has so far not evoked any significant responses. It is possible that with the great development of the temporal lobe in man the responsive cortex has been displaced more ventromedially than in the monkey (132). Patients are able to overcome partly the respiratory arrest when asking to count during the stimulation (132). The cessation of breathing is frequently associated with a feeling of tiredness and sleepiness and a tendency to close the eyes (132) and with impaired consciousness (132, 156).

ACCELERATION OF RESPIRATORY MOVEMENTS. Acceleration of breathing with increased, unaltered or decreased amplitude has been observed on stimulating the motor cortex of the cat (fig. 2*C*), dog and monkey (cf. 126). A second acceleratory area is found in the anterior ectosylvian and sylvian gyri in the cat (126, 234, 254) and dog (126) (fig. 2*C*). This area apparently coincides with the second somatosensory field (126). A third acceleratory zone has been located in the middle and anterior portion of the cingulate cortex in the dog (126, 147, 240), cat (126) (fig. 2*E*) and man (198). This acceleratory area appears to be located posterior to the zone yielding maximum inhibitory effects. In the anesthetized monkey the acceleratory response from the cingulate is very inconsistent, probably due to great susceptibility to anesthesia and to interference with the cerebral blood flow (126). It is readily obtained in unanesthetized animals (10) and in animals under light chloralose or chloralose-urethane anesthesia (126, 240); it disappears before the inhibitory effects which are the last to succumb on deepening the anesthesia (126). Acceleration appears to be more readily produced in dogs than in cats (126, 240) and monkeys (126).

Finally, acceleration of breathing, usually associated with a marked decrease in amplitude, has been recorded on stimulation of the rostral part of the pyriform (periamygdaloid) cortex in cats (126, 144), dogs (126) and monkeys (10, 166) in unanesthetized or lightly anesthetized (urethane, chloralose-urethane) preparations. The response can be converted into pure inhibition by additional administration of barbiturates (126). According to Koikegami & Fuse (144) the effect is mediated through the subjacent lateral amygdaloid nucleus and thence through the stria terminalis. As stimulation of all these structures in unanesthetized animals produces rapid sniffing (128), manifesting itself *inter alia* with increased rate and diminished respiratory amplitude, it is quite possible that the acceleration of respiration from the periamygdaloid cortex merely represents part of a complex pattern related to olfaction. The same is probably true of various other types of respiratory effects which can be produced upon stimulation of the olfactory pathways (126, p. 57; 241).

EFFECTS ON SPONTANEOUS, CORTICALLY AND REFLEXLY INDUCED MOVEMENTS AND MUSCULAR TONE. In 1944 Bailey *et al.* (23) included the anterior cingular region (area 24) in the so-called cortical 'suppressor' areas. Previously five such areas (8s, 4s, 3s, 2s and 19s) had been mapped on the lateral surface of the hemisphere of the monkey and cat [cf. reviews by Kaada (126, p. 93), Sloan & Jasper (230) and Druckman (58)]. The motor and electrical responses resulting from stimulation of these areas have been summarized as follows (60, 161): *a*) inhibition of motor after-discharges elicited by stimulation of any focus in the sensory-motor cortex, *b*) relaxation of existing muscular contractions, *c*) a rise of threshold and reduction of the motor response to stimulation of area 4, and *d*) a transient diminution of the electrical activity of area 4 (61) and of the entire cerebral cortex (81).

The two latter effects were characterized by a remarkably long latency of several minutes whereas the first two effects occurred rather promptly (82, 161), as did the cessation of spontaneous movements and the reduction of muscular tone observed by Hines (110) on stimulating area 4s. Later studies (58, 230) have revealed that the long-latency motor and electrical responses, which were originally elicited only from the specific cortical 'suppressor' strips, are most probably identical with the 'spreading depression' of Leão (148), a phenomenon which is nonspecific in the sense that it can be elicited from almost any portion of the cerebral cortex.

Eliminating the long-latency effects as characteristic responses to excitation of the cortical 'suppressor' areas, the prompt cessation of motor after-discharges and relaxation of 'existing muscular contractions' (including cessation of spontaneous movements) are the only two of the above-mentioned responses which, according to the literature, should be common to all these areas when examined under anesthesia. [For

these immediate effects the term 'suppression' should be discarded and the proper term 'inhibition' used (58, 126).] On the other hand, inhibition of spontaneous movements and of motor after-discharges has also been recorded on stimulation of areas outside the 'suppressor' strips of Dusser de Barenne and McCulloch. Thus, Tower in 1936 (254) obtained such effects by stimulation of the frontal, temporal and occipital respiratory inhibitory fields in cats under light ether anesthesia. In the monkey, a quieting effect on spontaneous movements has been produced from a rather diffuse zone of the lateral surface of the frontal lobe, comprising chiefly the intermediate region, areas 8s and 9 (111, 126, 172, 173), and from the junctional region of the parietal and occipital lobes with the superior gyrus of the temporal lobes (111, 126). There was, however, no loss in tone, either in cats or in monkeys, on stimulation of these areas. This is important to note because Tower's frontal field in cats includes the anterior cingulate region, electrical stimulation of which in monkeys under Dial anesthesia by Bailey *et al.* (23) has been said to provoke a "relaxation of existing muscular tension," and in the etherized monkey a "pronounced decrease in the resistance of the nonmoving extremity to passive movements to the point of flaccidity" (238). The knee jerk was abolished (238). This was confirmed by Ward (266). These discrepancies were further emphasized in the reports by Clark and associates (44, 45) who failed to find any evidence of inhibition of muscular tone by stimulation of the anterior cingulate cortex in unanesthetized dogs (44) or of the frontal eye field (area 8s) in unanesthetized monkeys (45). Kaada (126) has reinvestigated and further analyzed the influence of the cortical 'suppressor' areas, particularly the rostral cingulate region, on spontaneous movements, posture and tone, cortically induced movements and spinal reflexes in lightly anesthetized cats and monkeys. The presence of an orbitoinsulotemporal polar field, with quite similar inhibitory effects on respiratory movements as part of the anterior cingulate cortex, prompted the search for the possible inhibitory influence of this field on the various other kinds of somatomotor activities just mentioned. The results may be summarized as follows.

a) Effects on spontaneous movements and muscular tone. Spontaneous movements occurring under light anesthesia such as struggling and shivering and induced 'chloralose jerks,' could readily be inhibited by electrical excitation of all areas exerting an inhibitory influence on respiratory movements in the monkey, infant chimpanzee, cat and dog (the dotted areas in fig. 2*A* to *E*). Maximum quieting effect was obtained from the same two medial and basal fields which produced the strongest inhibition of respiration—one around the genu of the corpus callosum on the medial surface, and a second centering around the olfactory tubercle in the posterior orbital, anterior insular, rostral pyriform and adjacent temporal polar cortex of the monkey and the corresponding areas in the cat. Such movements could be held in abeyance, bilaterally, as long as the stimulus was applied and were usually resumed within a few seconds after cessation of stimulation. Inhibition of movements from these two optimum zones was associated with a widespread muscular relaxation as judged by the diminished resistance to passive movements of the extremities. Pre-existing postures were inhibited. Thus a rigidly extended or raised arm or leg became flaccid and slowly dropped; the knee jerk was abolished and the eyelids often closed as when the animal is going to sleep. The feeling of tiredness and sleepiness and the tendency to close the eyes on stimulation of the same area in conscious patients should be recalled (see above).

From the regions with weaker effects on the respiratory movements—such as a great portion of the anterior cingulate area, the lower part of the subcallosal region, the lower precentral region, parts of the orbitoinsulotemporal field, the retrosplenial region, and the separate lateral temporal field of monkeys, cats and dogs—the effect under light anesthesia was mainly one of arresting spontaneous random and rhythmic movements (fig. 4*B*, *C*) without loss of muscular tone. The eyes opened and the pupils dilated slightly, giving the animal an 'awaking' type of response or appearance of attentive repose or alertness. A similar quieting or 'arrest' reaction without any loss of tone has been obtained by weak stimulation of these areas through implanted electrodes in unanesthetized cats (118, 119, 126, 130, 131, 232, 269) and also from points within the so-called cortical 'suppressor' areas 8s, 2s, and 19s in lightly anesthetized cats (fig. 4*A* to *C*) and the intermediate zone of the lateral frontal cortex in the monkey (126). Frequently the inhibition of movements may outlast the stimulus for some seconds. This prolonged action is associated with a local electrical after-discharge at the site of stimulation with no spread into the motor cortical regions (126, 270).

b) Inhibition of motor after-discharges evoked by motor cortex stimulation. Motor after-discharges can be brought to a fairly abrupt halt or prevented, as shown in figure 4*D*, by stimulation of the areas in figure 2*A*

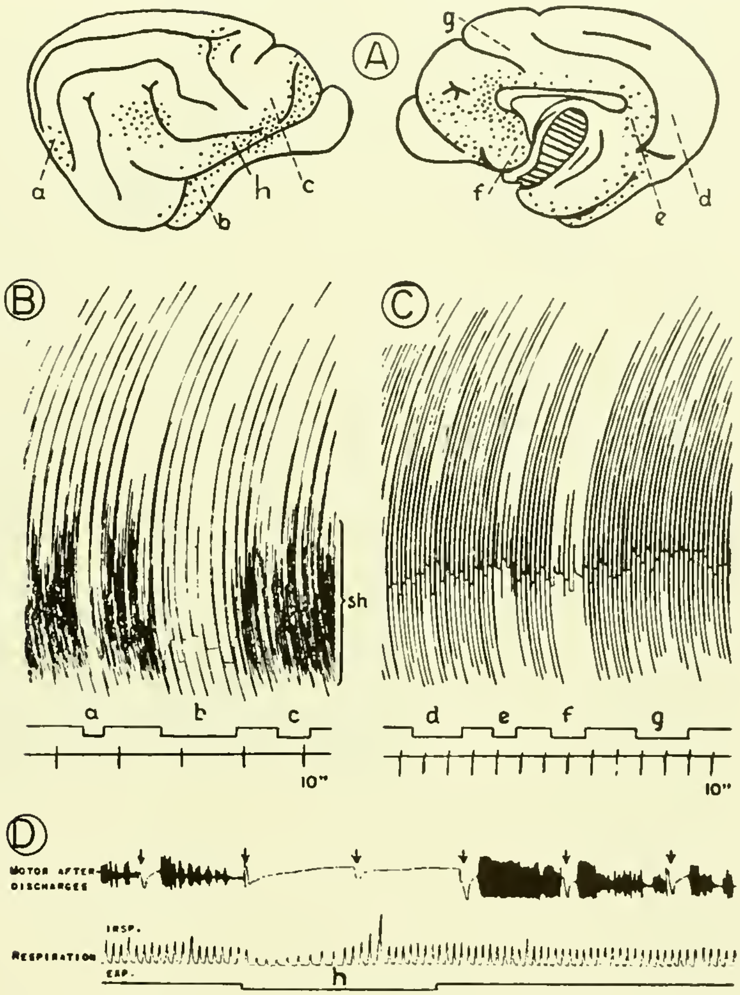

FIG. 4. *A: Stippled regions* represent areas of cat brain from which inhibition of spontaneous movements, 'chloralose jerks' and motor after-discharges were obtained on stimulation. *B:* Shivering (*sh*) superimposed on 'chloralose jerks' of the left leg elicited by intermittent tactile stimulation. *C:* 'Chloralose jerks' only. Weak stimulation of 'area 19s' (*a*) and the pyriform cortex (*b*) inhibits shivering. 'Chloralose jerks' inhibited from the retrosplenial (*e*) and subcallosal (*f*) regions. No effects on excitation of points (*c*), (*d*) and (*g*) outside the *stippled fields*. *D:* The left motor cortex was stimulated every 15 sec. (60 cps, 4 v., 3 sec.) and the resulting dorsiflexion of the right ankle (at *arrows*) was followed by local motor after-discharges. Inhibition of these after-discharges results from concurrent stimulation of the orbital gyrus (*h*). Motor after-discharges reappear after end of stimulation. [From Kaada (126).]

to *E* and figure 4*A* found to arrest spontaneous movements and 'chloralose jerks' in anesthetized monkeys and cats (126). The effects are less marked during more violent movements. The accompanying electrical after-discharges recorded from the motor cortex are quite unaffected. The most effective points are located within the two medial and basal fields yielding maximum inhibition of muscular tone and spontaneous movements.

c) Effects on cortically induced movements and spinal reflexes. The most extensive studies dealing with this topic are those of Hodes *et al.* (114, 185) on the cingulate cortex and subcortical structures in cat and of Kaada (126) on the cingulate and orbitoinsulotemporal areas in the cat and monkey. Excitation of the medial and basal areas exerting a bilateral inhibitory effect on spontaneous movements has been shown to influence single contractions induced by stimulation of the motor cortex and the knee jerk in three ways: by inhibition (fig. 5*D*), facilitation (fig. 5*C*), and facilitation changing to inhibition after brief stimulation (fig. 5*E*) (126). This inhibition appears rather promptly, attaining a maximum within a few seconds, and thus should be clearly distinguished from the long-latency response identified in the literature as 'suppression of motor response.' All three types of responses are usually associated with inhibition of spontaneous movements, including respiration; facilitation also appears with acceleration of breathing (126).

The areas inhibiting cortically and reflexly induced movements approximately coincide with those yielding strongest inhibition of respiratory and other spontaneous movements and muscle tone, i.e. the cortex surrounding the genu of the corpus callosum (114, 126) and the orbitoinsulotemporal polar field as outlined above (indicated by vertically hatched areas in fig. 5*A*, *B*) (126). The third type of response,

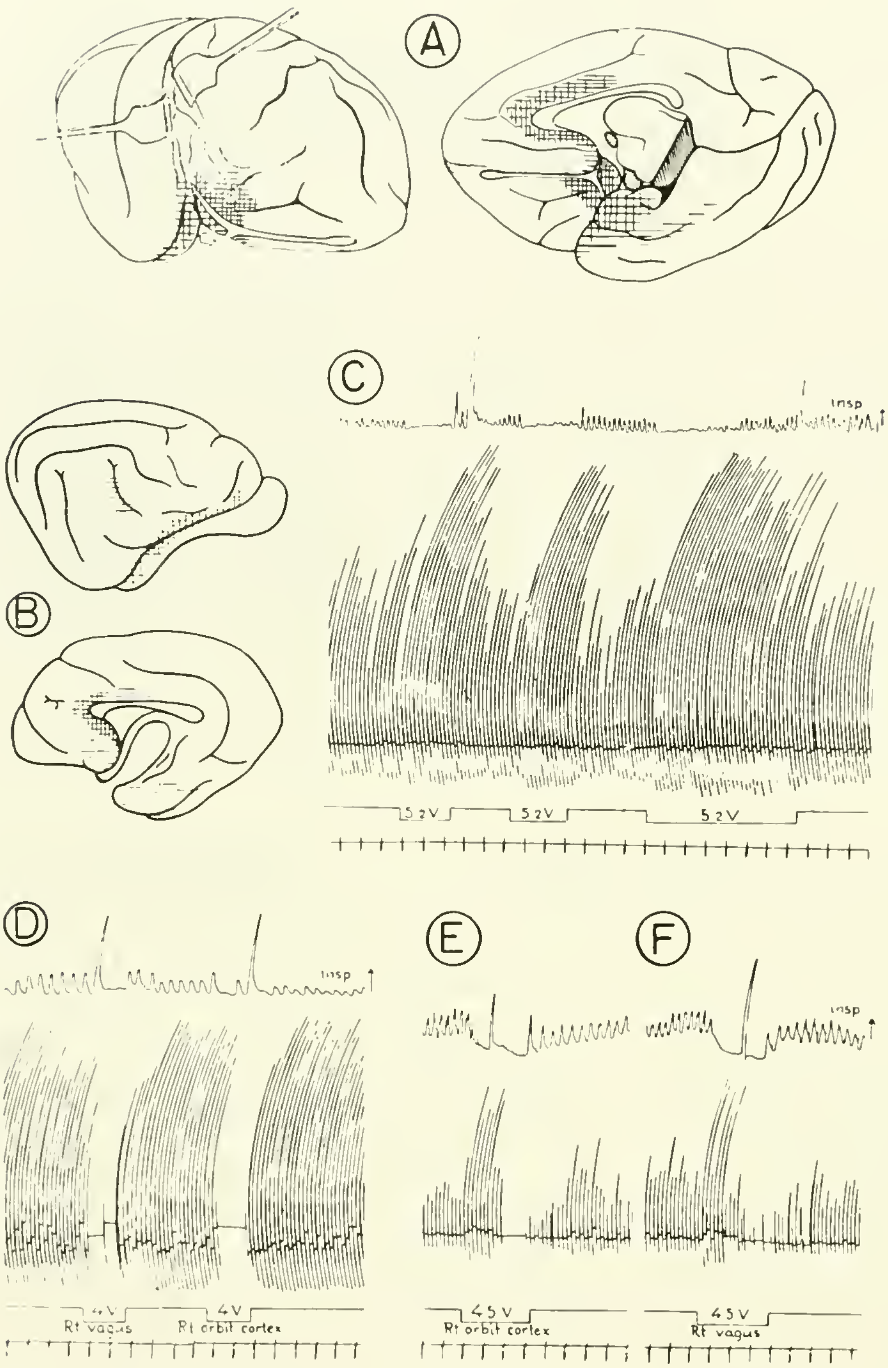

FIG. 5 Areas facilitating (*horizontal lines*) or inhibiting (*vertical lines*) cortically induced movements and the knee jerk in monkey (*A*) and cat (*B*). *C* to *F*: *Upper tracing*, respiratory movements; *second tracing*, the knee jerk elicited every 2 sec. in cat. Time, 10 sec. Respiratory inhibition associated with facilitation (*C*), inhibition (*D*), and facilitation reversing to inhibition (*F*) of the knee jerk on stimulating the orbital gyrus in different experiments. *D* and *F*: Stimulation of the central end of the cut vagus nerve produces identical effects in the respective experiments. [From Kaada (126).]

facilitation reversing to inhibition, was obtained from the same zones (126). The extent of the areas inhibiting cortically induced movements was greater than that reducing the knee jerk (114, 126). Facilitation has usually been obtained from the horizontally hatched regions in figure 5A, *B* outside these 'inhibitory' areas, i.e. from the regions producing the 'awakening' or 'arousal' type of response in unanesthetized and lightly anesthetized animals, while occasionally facilitation (particularly of cortically induced movements) also occurred, in quite an unpredictable manner, on stimulation of the medial and basal 'inhibitory' zones (126). The increase of the knee jerk was inconsistent and usually less marked than the facilitation of cortically induced movements. Thus, there were a number of cortical points, particularly in the anterior

cingulate region, which facilitated cortically initiated movements without influencing the knee jerk (126, 185). Facilitatory responses appear to be favored by chloralose and may at times be converted to inhibition by additional administration of barbiturates (126). No reversal of the effects has been obtained by varying the stimulus characteristics (126). Both facilitation and inhibition are independent of accompanying respiratory or arterial pressure alterations (126). They are exerted upon flexor and extensor movements indiscriminately (58, 126) and in a nonsomatotopic manner (126). The effects are present also in mono- and polysynaptic reflex discharges of the ventral spinal roots (126). Like most other central motor areas the medial and basal inhibitory and facilitatory zones influence the intrafusal fibers of the muscle spindles through the small-sized γ-motoneurons prior to their effect on the large-sized α-motoneurons of the ventral horn (94).

Regarding the site of the facilitatory and inhibitory action, both may be produced in the absence of any alteration of the electrical activity in the motor cortex (58, 126, 232) or after removal of the cortical sensory-motor areas (126, 232). However, besides acting directly 'downstream,' facilitation of cortically induced movements may also be obtained at a cortical level, dependent on corticocortical connections (126, 232).

The similarity of the inhibition of somatomotor activities obtained from the most sensitive two medial and basal cortical zones herein discussed to that produced by stimulation of the central end of the cut vagi (as shown in fig. 5*D*, *F*) has been emphasized (126, p. 137). The orbital surface of cats and monkeys has been considered as a sensory-motor vagus representation; excitation of the vagus nerve may influence the electrical activity in this cortical area (18, 55, 56, 116), and various autonomic responses, such as alterations in arterial pressure and gastrointestinal motility, apparently similar in every respect to those obtained by direct central and peripheral vagus stimulation, can be provoked from this cortical field (see below). It is believed (126, p. 137) that the inhibition of somatomotor activities produced from the orbital surface merely represents one of the many 'vagal' activities which this region seems to display. Afferent impulses in the vagi and descending impulses from the cortical vagus motor field apparently act upon the same brainstem mechanism producing similar visceromotor and somatomotor responses. The demonstration of identical autonomic and inhibitory somatomotor effects from the anterior insula and temporal pole in monkeys has suggested that the cortical vagus representation also extends into these zones and, further, that a 'second' vagus representation resides in the genual portion of the anterior cingulate cortex (126). Regarding the proposed second vagal representation in the latter area, it is relevant to recall the recent demonstration of an afferent vagal projection to the pre- and subgenual portion of the anterior cingulate area (55, 56, 116). This ascending path courses through the anterior hypothalamic, preoptic and septal areas, as does possibly the descending path mediating the 'vagal' visceral and the somatic inhibitory effects from the same cortical zone (cf. below).

The type of response consisting in facilitation of cortically and reflexly induced movements associated with inhibition of respiration, other spontaneous movements (as shown in fig. 5*C*), and motor after-discharges—is quite similar to that induced from parts of the thalamic reticular system (13, 117, 120; 126, p. 158). It seems likely that both quieting of prestimulatory spontaneous movements and the facilitation represent integrated parts of the complex 'awakening,' 'arousal' or 'attention' response which can be produced on high-frequency stimulation of these cortical and thalamic areas in unanesthetized animals. The 'arousal' seen in the electrocorticogram and the pupillodilation on stimulating the same areas provide further support for this assumption. The brain-stem activating system can be influenced not only by peripheral ascending impulses, as first demonstrated by Moruzzi & Magoun (182), but also by corticofugal impulses from these medial and basal areas of the forebrain (70; 126, p. 240). These areas appear to share this 'arousal' function with the lateral frontal, occipital and temporal fields, stimulation of which has been shown to exert a similar quieting effect on spontaneous movements (figs. 2, 4*A*). There seems to be a close coincidence between these areas and those recently shown to project into the brain-stem reticular system (70). The same areas also cause a similar 'arousal' of the electrocortical activity (126, 225; Kaada & Johannessen, unpublished observations) and of the behavior of the nonanesthetized animal by stimulation through implanted electrodes (118, 119, 130, 131, 223; Fangel & Kaada, unpublished observations).

The apparently contradictory results reported by various authors regarding the 'suppression' of motor responses on anterior cingulate stimulation are possibly due to the fact that various overlapping portions inside this area subserve different functions and therefore respond differently. One portion appears to be

related to 'vagal' activities and inhibits cortically and reflexly induced movements; another portion seems to be related to the 'arousal' mechanism and facilitates cortically initiated movements. Arrest of prestimulatory somatic movements is common to the two different patterns of activity and may possibly have a different functional significance in the two patterns. The cortically induced 'arousal' appears to be rather sensitive to anesthesia (126, 225; Fangel & Kaada and Kaada & Johannessen, unpublished observations) and thus it may be that stimulation of a given point may facilitate a cortically induced movement in the unanesthetized or lightly anesthetized animal, whereas the same stimulation may cause inhibition after the 'arousal' paths have been blocked by anesthesia. Inhibition from the anterior cingulate and orbitoinsulotemporal 'vagal' zones may persist into the deepest stages of anesthesia (126). The conversion of respiratory acceleration to inhibition by administration of barbiturates, mentioned previously, and the reversal of arterial pressure response from decrease to increase after vagotomy (240) may possibly be similarly explained.

The inhibition of respiratory and other spontaneous movements and of muscular tension by excitation of the olfactory pathways in the uncal region are possibly related to the sense of smell as inhalation of various vapors and irritants may cause a similar profound inhibition of movements and muscular tone (6, 11, 67).

The possible corticosubcortical routes mediating the inhibitory (including respiratory) and facilitatory somatic effects evoked from these cortical zones have been discussed in detail elsewhere (126, pp. 146–160). Although not yet proved, there is some experimental evidence for a hypothalamic route (possibly through the ventromedial hypothalamic nucleus) for the inhibitory influences from the medial and basal 'vagal' cortical zones yielding optimum inhibitory effects. This nucleus appears to represent a focal area for a number of fiber systems concerned with the control of autonomic functions (46) and with inhibitory effects on somatomotor activities (126, p. 153). Direct stimulation of the ventromedial nucleus produces a strong inhibitory influence on spontaneous, reflexly and cortically induced movements (13) as does stimulation of the anatomically demonstrated projections to this nucleus from the posterior orbital surface via the preoptic region and medial forebrain bundle (46, 215), from the olfactory tubercle (49), from the pyriform cortex via the amygdala (126, 144) and stria terminalis (13, 126, 144), and from the anterior cingulate and subcallosal cortex via the septal and preoptic areas (13, 91, 101, 102, 135, 170, 265). The recent studies by Turner (256), concerning the respiratory inhibitory path from the posterior orbital surface, and by Hodes *et al.* (114), concerning the path for bilateral inhibition of the knee jerk from the rostral portion of the anterior cingulate cortex, are consistent with this assumption. More caudally the respiratory inhibitory effects from the orbital cortex are carried downward, possibly by a bifid pathway, to the reticulum of the pontine brain stem outside the caudate nucleus (256). According to Poirier & Schulmann (195) the respiratory (and arterial pressure) effects evoked from the temporal pole are dependent on a path coursing ventrolateral to the optic tract towards the pulvinar.

The weaker inhibitory effects on respiratory and other spontaneous somatic movements (associated with the 'arousal' response, without loss of muscular tone) obtained from the more extensive medial and orbitoinsulotemporal zones are possibly mediated via the thalamic and brain-stem reticular system (118, 119, 126). The same appears to be true of the bilateral facilitatory effects on cortically induced movements (126, p. 156; 185).

TONIC AND CLONIC MOVEMENTS. Slow tonic movements of the limbs, trunk and neck, mostly extensor and contraversive in type, have been observed by various investigators on stimulating the anterior cingulate (126, 147, 232, 266), subcallosal (126), posterior orbital (126, 215), anterior insular and temporal polar cortex (73, 126, 133) in anesthetized animals. Showers & Crosby (227) describe a pattern of somatotopic movements obtained by stimulation of the anterior cingulate region which may be elicited in a reversed order from the stimulation of the posterior cingulate region. The elicitation of such movements requires a light level of anesthesia and they most likely represent fragments of the more complex movement patterns seen on stimulating the same areas in nonanesthetized animals (103, 118, 119, 126, 130, 131, 232). The movements may be induced after bilateral ablation of the motor areas (126, 232) and cannot be attributed to either spread of current or reaction to pain (215).

Twitching of the facial musculature and, occasionally, jerky movements of the neck and shoulders have been observed on stimulation of the anterior cingulate (126, 153, 232) and anterior pyriform cortex and the amygdala (25, 126, 246, 258).

Tonic contraversive turning of the head and usually also of the eyes is frequently seen in temporal lobe

seizures and is of special diagnostic importance, as it is often the only clinical manifestation to indicate the side of the lesion (169). In the unanesthetized, freely moving cat a similar immediate tonic contraversion can be induced from the periamygdaloid cortex and parts of the subjacent amygdala (83, 87, 126, 128, 166, 258). This tonic contraversion is not to be mistaken for the contraversive searching movements seen in the 'arousal' response. It appears likely that tonic contraversion in most, if not all, temporal lobe seizures is due to the involvement of these structures in the epileptic discharge. The same applies to the general rigidity and tonic extension of one or both contralateral limbs, the twitching of the face (usually ipsilateral) and the slow jerking movements of the limbs frequently encountered in temporal lobe seizures (25, 127, 258).

VOCALIZATION, CHEWING, LICKING AND SWALLOWING MOVEMENTS. Vocalization resembling the sounds which a monkey daily emits has been produced by Smith by stimulation of the anterior portion of the cingulate (235, 238) and hippocampal gyri (237). This has been confirmed in the monkey (fig. 6*A*) (126, 227, 232) and dog (44, 147). Ward (266), however, failed to obtain vocalization in monkeys and no such responses have been obtained in cats. EEG records taken during vocalization (232) showed no change as might be expected if vocalization had been a reaction to a painful stimulus. The response disappears after deepening the anesthesia and after local application of novocaine to the site of stimulation, and it persists after bilateral ablation of the cortical areas for vocalization in the lower precentral region (126).

According to Kaada (126) and Sloan & Kaada (232), vocalization can be elicited from the medial surface only in an area limited to the forward upper portion of the anterior cingulate region and to the banks of the cingulate sulcus (fig. 6*A*). In man, similar vocalization has been evoked by stimulation of the 'supplementary motor area' above this sulcus (33, 190). The possibility that the zone yielding vocalization in monkeys represents the homologue of the 'supplementary motor area' of man should be considered (232).

Rhythmic well-coordinated chewing movements have been produced from the rostral pyriform cortex and amygdala in monkeys (126, 166) (fig. 6*A*), cats and dogs (126, 207, 246). This mastication usually occurs after a surprisingly long latency of some 10 to 15 sec. (126, 128) which is also characteristic of mastication in temporal lobe seizures (169, 187, 188).

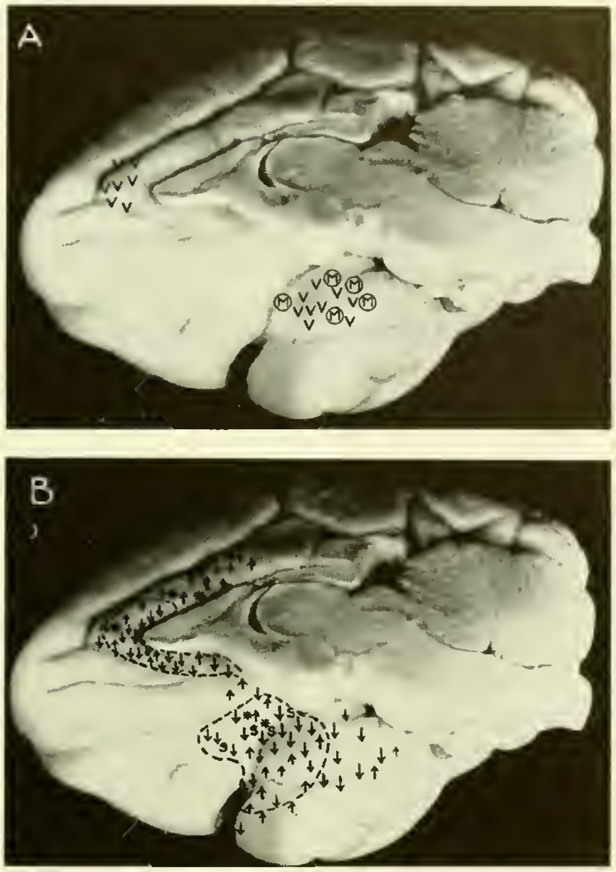

FIG. 6. Ventromedial views of the right hemisphere of *Macaca mulatta*. *A*: Points from which vocalization (*V*) and mastication (*encircled M*) were produced by electrical stimulation. *B* Points from which a rise (↑) or drop (↓) in arterial pressure, salivation (*S*) or piloerection (*) were obtained. The two *zones* encircled by *dotted lines* indicate areas from which alteration in pyloric antral contractions was obtained by stimulation. [From Kaada (126).]

Swallowing and licking movements and retching have been elicited from the same areas as well as from the olfactory tubercle (126, 207). These responses are all independent of the precentral motor cortex (126) and fornix (246). The masticatory response possibly is mediated from the pyriform cortex via the amygdala and stria terminalis (126).

Autonomic Responses

CARDIOVASCULAR ALTERATIONS. It is a well-established fact that the cardiovascular system can be influenced from the motor and premotor and other cortical areas outside those treated in this chapter [cf. Kaada (126)]. Spencer (241) was the first to report arterial

pressure alterations on excitation of the orbital surface of the frontal lobe. Smith (237, 238) evoked similar responses from the rostral portions of the cingulate and hippocampal gyri and Kaada *et al.* (133) from the anterior insular and temporal polar cortex in monkeys. These findings have been confirmed and further analyzed in various species of animals. Rises as well as falls in arterial pressure have been recorded in the cat, dog and monkey on stimulating the anterior cingulate cortex (10, 107, 126, 133, 147, 238–240), the orbital surface (21, 54, 107, 126, 133, 159, 215, 240, 241), the anterior insula (115, 126, 133), the rostral pyriform (10, 126, 133, 146, 195, 237, 239, 263) and adjacent temporal polar cortex (10, 126, 133, 195, 263). Similar effects have been obtained in man from the anterior cingulate (198), posterior orbital surface (41, 42, 158) and temporal pole (40, 42).

The two most sensitive regions on the medial and basal surfaces appear to coincide with the optimum zones for inhibition of respiratory movements and gastric motility in the monkey (the areas encircled by broken lines in fig. 6*B*), dog and cat. According to Poirier & Schulmann (195) the low-threshold cardiovascular temporal zone extends farther backward than indicated on figure 6*B* and includes about one third of the medioventral portion of the hippocampal gyrus. In the cat and dog the most sensitive spots are similarly found in the pre- and subgenual region and in the orbital and adjacent rostral pyriform cortex and olfactory tubercle.

Most authors have reported a fall in pressure as the most frequent response from these two zones in the various animals and under a variety of anesthetics. The fall may amount to 15 to 30 mm Hg, or even up to 60 mm (126, 240, 263). It occurs almost instantaneously (fig. 3*B*) and may or may not be associated with a slowing of the pulse rate. The initial decline may be followed by a secondary small rise above normal. Initial arterial pressure elevations rarely exceed 40 mm Hg and occur after a latency of 2 to 8 sec. (fig. 3*A*). From the temporal pole rather prolonged arterial pressure alterations may be induced (263).

The character of the response seems to depend on several factors. *a*) The site of stimulation may be critical. Pressor and depressor points have been located only a few millimeters apart. However, usually one type of response predominates from all points within a given area under the same experimental conditions. In the same animal the orbital surface and olfactory tubercle may yield opposite effects (215) and the same may be true when comparing the posterior orbital surface and the temporal pole (263). *b*) The level and type of anesthesia are important. Deepening the anesthesia sometimes seems to favor depressor responses (126); further, under curare (215), light ether (10, 241), pentobarbital (21) or thiopental (42, 158) anesthesia, pressor responses predominate on stimulation of the orbital surface whereas depressor effects are usually encountered under diallyl barbituric acid (Dial) anesthesia (54, 215). *c*) Occasionally a frequency-conditioned reversal of the arterial pressure effect has been observed (126, 215), but as a rule the direction of the change is independent of the stimulus frequency; both falls and rises may be obtained over a wide frequency range, with only the degree of the response varying (usually optimum at 30 to 60 cps and prolonged pulse durations of 10 to 20 msec.). *d*) Stimulus strength alterations may also yield reversals. Hess *et al.* (107) obtained arterial pressure fall and respiratory inhibition on weak stimulation of the anterior cingulate cortex in cats, whereas stronger stimulation yielded the reverse. *e*) Animals of different species may react differently. Rises in arterial pressure induced from the orbital surface in animals anesthetized with diallyl barbituric acid seem to be more readily obtained in the monkey than in the cat (215, 241).

The arterial pressure effects are not secondary to the associated respiratory changes (42, 126, 215, 238), and there is no constant relationship between the direction of the respiratory and arterial pressure responses (126, 215, 238). Section of the trigeminal nerves does not alter the arterial pressure responses from the cortical areas concerned (115, 126). Bilateral vagotomy abolishes or greatly reduces the depressor responses from the anterior cingulate (126, 238, 240), the orbitoinsular cortex (126) and temporal pole (126, 237). On the other hand, the pressor responses persist after vagotomy (16, 126, 240). Since some fall in arterial pressure still may be obtained after bilateral vagotomy (115, 126, 215), a dilatation of the peripheral blood vessels through some extravagal route must also be assumed to occur. Peripheral effects have been observed by Delgado & Livingston (54) who recorded a marked rise in the skin temperature of the limbs on excitation of the posterior orbital surface in monkeys. According to Sachs *et al.* (215) arterial pressure changes (and respiratory arrest) produced from the same area persist after bilateral cervical vagotomy, splanchnicectomy and adrenalectomy, and after destruction of the hypothalamic paraventricular nuclei. Physostigmine prolongs the cardiac inhibition

from the anterior cingulate and pyriform cortex (238, 239).

Little is known regarding the descending pathways mediating the arterial pressure effects to the cardiovascular centers of the lower brain stem. A drop in arterial pressure has been obtained from a zone extending from the genual portion of the anterior cingulate cortex and through the septal, preoptic, hypothalamic and mesencephalic areas (102, 136). This 'path' appears to coincide closely with that yielding inhibition of cortically and reflexly induced movements and respiration (discussed above). According to Wall & Davis (263) the anterior cingulate cortex may possibly influence arterial pressure by a mechanism dependent on the anterior temporal lobe. Bilateral hypothalamic lesions may abolish the arterial pressure response from the orbitoinsular cortex without influencing the respiratory response (263). Lund (160) has traced a pressor zone from the base of the forebrain to the septum pellucidum. Arterial pressure effects evoked by stimulation of the temporal pole are possibly mediated via a bundle of fibers which travel with the temporopontine tract to the tegmentum and pons (263) or to the pulvinar (195). Section of the fornix (126) and pyramidal tract (263) leave the arterial pressure responses induced from the medial and basal cortical areas unaltered.

GASTRIC MOTILITY. On the lateral surface of the cerebral hemisphere two areas with influence on gastrointestinal motility have been located, one in the intermediate frontal cortex and a second in the parietal lobe. [These have been considered in previous reviews (16, 55, 63, 83, 126).]

In 1940 Bailey & Sweet (21) recorded a fall in tone of the stomach wall on stimulation of the posterior orbital surface of the frontal lobe of monkeys and of the orbital gyrus of cats. The gastric influence of this area was subsequently studied by Babkin *et al.* (14–16) in the dog, by Eliasson (63) in the cat, and by Kaada (126) and Hoffman & Rasmussen (115) in the monkey. In the latter species alteration in pyloric antral contractions also was obtained by stimulation of the anterior insula, the olfactory tubercle and the tip of the temporal lobe, i.e. the basal continuous cortical zone yielding optimum inhibition of respiratory and other somatomotor activities and arterial pressure changes (the lower encircled area in fig. 6*B*). This finding emphasizes further the homology between the cortex of the orbital gyrus of cats and dogs and the orbitoinsulotemporal cortex in the monkey (see above).

From the medial surface gastric motility can be influenced by stimulation of the anterior cingulate region in dog (14, 16), cat (63) and monkey (126). In the dog and cat the responsive region is confined to a rather small area in the pre- and subcallosal portion of the anterior cingulate cortex; the corresponding area in the monkey is indicated in figure 6*B*.

Only inhibition of pyloric peristalsis has been obtained in all species of animals from the anterior cingulate cortex. In the cat this inhibition may be associated with a moderate augmentation of the fundic motility (63). Optimum stimulus parameters are frequencies of 30 to 60 cps and prolonged durations of 10 to 20 msec. for all species of animals. Stimulation of the anterior cingulate cortex in humans may be associated with plainly audible borborygmi and violent passage of gas by rectum (197). The effects obtained from the orbitoinsulotemporal polar cortex are essentially similar to those evoked from the anterior cingulate except that no augmentation of fundic motility has been reported on stimulating the former area. Further, increase of the stimulus frequency shortens the latency of the orbital response, while it influences only the degree of the effect produced by cingulate stimulation (15).

Occasionally some augmentation of pyloric peristaltic contractions has been observed in dogs (15) and monkeys (126) on stimulation of the orbitoinsulotemporal polar field. This effect may possibly have been caused by spread of excitation to the neighboring olfactory pathways (the olfactory bulb and tract, rostral pyriform cortex), stimulation of which, according to Eliasson (63), results in strong contractions and increased peristalsis of the stomach.

The induced alterations in gastric motility are not caused by concomitant changes in respiratory movements or arterial blood pressure (14–16, 63, 126). The anesthetic commonly used by all observers has been chloralose, either alone or in combination with urethane or barbiturates. The effects are similar under barbiturates or ether alone (16, 126). Chloralose appears to augment gastric motility by stimulating the vagal centers in the lower brain stem (14). This may account for the difficulties of some observers in obtaining increased contractions by cortical stimulation, as the experiments may have been performed under conditions of maximal motility.

Bilateral cervical vagotomy eliminates the gastric effects evoked from the anterior cingulate (14, 16, 63, 126) and orbitoinsulotemporal polar fields (14, 16, 63, 115, 126), while section of the splanchnic (14, 63, 126) or trigeminal (115) nerves leaves the responses

intact. Atropine abolishes the cortically induced responses (63). These observations support the supposition of a dual vagal representation on the medial and basal aspects of the cerebral hemisphere (cf. above). Each of the two areas may exert its influence on gastric motility in the absence of the other (14, 63, 126). Cholinergic fibers running in the splanchnic nerves are responsible for the increase of gastric motility evoked by stimulation of the olfactory pathways (63).

The available data give no definite answer to the question whether the responsive cortical fields act directly on the dorsal motor nucleus of the vagus in the medulla oblongata or whether the impulses are transmitted through some intermediate station. Eliasson (63) has traced a pathway mediating the augmentatory effects from the olfactory bulb and tract and pyriform cortex through the amygdaloid nuclear complex. The fibers mediating the effects from the orbital surface pass, according to the same author, caudally and medially through the internal capsule below the anterior commissure. A discrete pathway has further been traced from the anterior cingulate cortex to the vicinity of the anterior commissure (63). It appears that these paths from the orbital and anterior cingulate areas coincide with those mediating the cardiovascular and somatomotor inhibitory effects from the same areas through the hypothalamus (cf. above). The excitatory effects on the fundus of the stomach evoked from the rostral cingulate region are possibly mediated via the responsive area of the motor cortex as they are abolished by ablation and facilitated by strychninization of this area (63).

The general subject of nervous control of digestive processes is considered by Eliasson in Chapter XLV of this *Handbook*.

PUPILLARY RESPONSES. Pupillary dilatation, usually of a slight degree and associated with opening of the eyes, may, according to Kaada (126), be obtained from all cortical regions yielding inhibition of respiratory and other spontaneous somatomotor movements in monkeys (fig. 2*A*, *B*), cats (fig. 2*C* to *E*) and dogs. These rather extensive zones correspond well with the pupillomotor areas outlined in cats by Hodes & Magoun (113). On the medial surface an optimal zone has been found in the precallosal part of the cingulate gyrus of the cat (229). Pupillary dilatation was also observed by Smith (238), Ward (260) and Showers & Crosby (227) on stimulating the rostral cingulate cortex, by Showers & Crosby (227) from the posterior cingulate cortex, and by Sachs *et al.* (215) from the posterior orbital gyrus in the monkey. The response has been said to be due to oculomotor inhibition (113), or sympathetic excitation (266), or both (229).

Points yielding pupillodilatation were traced caudally by Hodes & Magoun (112, 113) in an uninterrupted column from the medial and ventral cortical zones through the basal telencephalon to the hypothalamus. In addition the septum, the mid-line group of thalamic nuclei, the subthalamus and a large part of the midbrain were found to yield similar responses.

The functional significance of the pupillodilatation evoked from these widespread cortical areas is obscure. It possibly represents an integrated part of the complex 'arousal' response which in the unanesthetized animal can be produced from the same cortical areas and which always is associated with some pupillodilatation and opening of the eyes.

Pupilloconstriction has been obtained in cats by stimulation of a narrow zone, 2 to 3 mm broad, immediately surrounding the genu of the corpus callosum (113, 126). At the thalamic and hypothalamic levels constriction of the pupils as a result of stimulation has, according to Hess (106), been observed only in association with drowsiness or sleep and with adynamia. Since the portion of the cingulate cortex yielding pupilloconstriction appears approximately to coincide with the optimum zone yielding sleep-like reactions with inhibition of somatomotor activities and autonomic 'vagal' responses (cf. above), it may be that this cortically induced pupilloconstriction has a functional significance similar to that of the hypnogenic-adynamic areas of the rostral brain stem.

OTHER AUTONOMIC RESPONSES. Piloerection has been induced by stimulation of the anterior cingulate (126, 227, 238, 266) and olfactory tubercle (126) in monkeys but no such effect has been seen in cats as a result of cortical stimulation (113, 126).

Salivation has been produced on stimulation of the cingulate cortex (227), the olfactory tubercle and pyriform cortex (126, 207) and the adjacent posterior orbital and anterior insular regions (fig. 6*B*) (126). Edinger's (62) suggestion that the olfactory tubercle is *ein Centrum des Oralsinnes* should be borne in mind.

Bladder contraction has been observed on stimulation of the posterior portion of the cingulate cortex in dogs (147) and of the pyriform area in monkeys (126, 239), cats and dogs (126). Henneman (98) recorded both contraction and relaxation of the bladder from these areas in cats.

Defecation has occasionally resulted from excita-

tion of the posterior part of the pyriform cortex in cats, dogs and monkeys (126). The descending paths mediating these effects from the pyriform area possibly course via the amygdala and stria terminalis (126).

For further details concerning the various autonomic effects evoked from these areas the reader is referred to the reviews by Gastaut (83) and Kaada (126).

Behavioral Responses

A behavior change termed 'arrest reaction' (126, 232), 'searching,' 'attention' (118, 119, 130, 131) or 'arousal' (223) can be elicited on stimulation of the regions indicated in figure 7*D* on the medial surface of the hemisphere in freely moving unanesthetized animals. The responsive sites are located mainly within the medial orbitofrontal cortex and the cingulate gyrus, including the anterior and posterior cingulate areas and the retrosplenial region. Finally, some points are found within the medial portion of the hippocampal gyrus, including the temporal pole (131) and in the orbital gyrus (126). The response shown in figure 7*A* and *B* is a rather typical one. Immediately at the onset of stimulation all spontane-

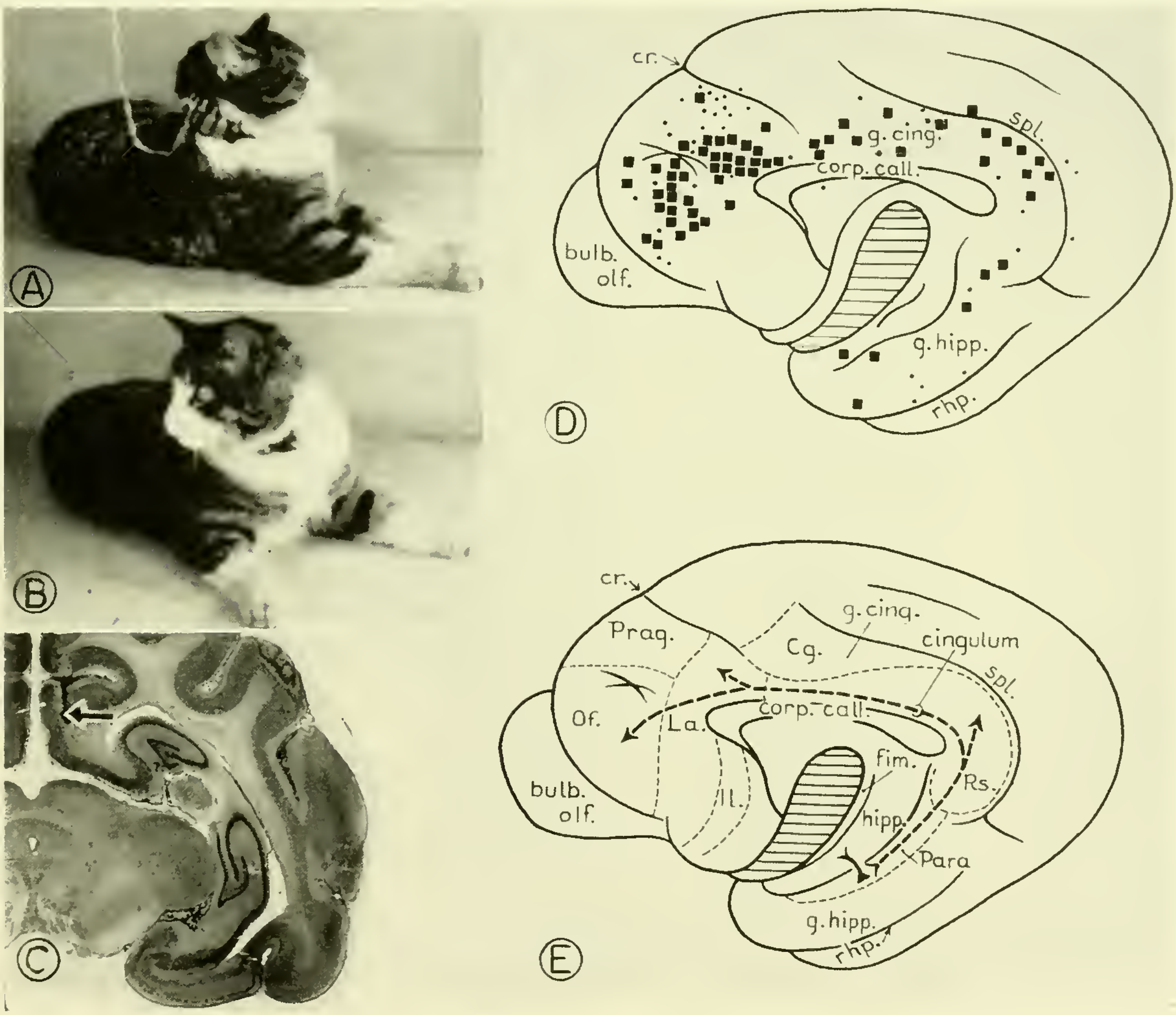

FIG. 7. *A* and *B:* 'Attention' or 'arousal,' raising of head, pricking of ears and searching movements to the right side caused by stimulating at point indicated by *arrow* (*C*) in the left retrosplenial region. [From Kaada *et al.* (131).] *D:* Medial aspect of cat hemisphere indicating points (*squares*) from which the 'attention' or 'arousal' reaction was obtained; no such responses from points marked by *dots*. *E:* Areal subdivision of the medial surface, mainly according to Rose & Woolsey (209). Origin and course of the fibers of the cingulum bundle is according to current concept. [From Kaada *et al.* (131) and Jansen *et al.* (119).]

ous occupation such as walking or licking ceases; the facial expression changes to one of 'attention' or 'arousal,' perhaps associated with some surprise, bewilderment or anxiety; the animal raises its head, the eyes open and the pupils dilate; there are slight pricking movements of the ears and quick anxious glancing movements of the eyes and head, usually to the contralateral side. This searching may result in circling movements to the side opposite that stimulated. The animals appear to be alert during the stimulation and respond adequately to various types of external stimuli. However, the reaction to such stimuli frequently seems to be decreased, the animal's attention apparently being fixed on 'something else.' It seems likely that the contraversive movements of the head and deviation of the eyes, both with a surprisingly long latency, observed by Hess (103) on excitation of the anterior part of the cingulate and of the medial orbitofrontal cortex, represent part of the same phenomenon. Similar behavioral arousal has recently been obtained in the monkey on stimulation of points in the anterior cingulate and temporal polar cortex (223). Responsive sites were also located in the superior gyrus of the temporal lobe, the orbital surface, the intermediate frontal cortex (frontal eye-field), parts of the sensorimotor cortex and the paraoccipital region.

It is of considerable interest that all these points from which behavioral 'arousal' has been induced in the awake cat and monkey appear to be situated within the regions shown in the anesthetized animal to exert an inhibitory influence on spontaneous movements (cf. above). The initial arrest of prestimulatory somatic activities with cessation of all movements in execution without any loss of muscular tone constitutes a most conspicuous feature of the 'searching' or 'arousal' response. Also, other isolated phenomena which have been recorded in the anesthetized animals, such as the pupillodilatation, the arterial pressure rise and the facilitation of cortically induced movements, possibly represent fragments of the total complex 'arousal' response seen in the freely moving animal.

At subcortical levels apparently similar behavioral arousal has been produced from part of the amygdala (86, 87, 128, 129, 166), the hippocampus (12, 130, 131, 166), the perifornical and posterior hypothalamic regions (104, 105), the dorsomedial and anterior thalamic nuclei, the intralaminar nuclei of the thalamus (5) and from other parts of the brain-stem reticular system (223). The behavioral arousal evoked from the medial orbitofrontal and cingulate cortex persists after bilateral destruction of the cingulum bundle, hippocampus, habenulae, striae medullaris thalami, amygdala and a number of the other brain-stem nuclei. It is abolished following lesions of the anterior basal part of the internal capsule and of portions of the intralaminar nuclei, suggesting the involvement of the thalamic reticular system in the cortically induced arousal (119). Physiological and anatomical evidence for an intimate relationship between the cingulate, subcallosal and orbitoinsulotemporal polar cortex and the thalamic reticular and the brain-stem activating system has been given in several studies (70, 95; 126, pp. 156 and 238; 200, 210, 231).

Reactions of fear have been produced in man on stimulating the anterior temporal cortex, particularly along the anteromedial portion of the first temporal convolution and periamygdaloid region (187). In animals fear and rage reactions, not uncommon manifestations of temporal lobe seizures (65, 84, 187, 188, 271), have been elicited from the amygdala (86, 129, 134, 166). According to Gastaut *et al.* (83, 86) fear reactions merge into rage on increasing the stimulus strength. However, the recent study by Ursin and Kaada (257a) indicates that the two phenomena in cats may be induced independently of each other from two separate, partly overlapping zones within the amygdala and not from the periamygdaloid cortex itself. It seems likely that in epileptics a discharging lesion in the anterior temporal cortex may cause these symptoms by spread to the amygdala through the rich connections known to exist between the two structures. Also, the behavior automatism (with unresponsiveness, confusion, masticatory movements, and inappropriate but often elaborate behavior and amnesia) which has been reproduced in epileptics on stimulating points centering in the periamygdaloid region (65, 66, 123, 169, 187) is possibly caused by spread of the abnormal discharges through the amygdala or the hippocampus to the brain stem. (This matter is considered in the succeeding chapters on the hippocampus and amygdala in this *Handbook*.)

Effects on Electrocortical Activity

The spontaneous electrical activity recorded from the cingulate and orbitoinsulotemporal polar cortex in the awake or anesthetized animal does not differ essentially from that recorded from neocortical areas, except that no intermittent 'barbiturate spindles' at a frequency of 6 to 12 per sec. are present in the pyriform cortex (99, 126).

Since 1950 several papers dealing with the effects of stimulation of these medial and basal cortical regions on the electrocorticogram have appeared. These effects are all apparent immediately at the end of stimulation. This is in contrast to the so-called 'suppression of electrical activity' with a latency of several minutes (61). As already discussed, the latter has been demonstrated to be identical with the nonspecific phenomenon of 'spreading depression' which is not related to any particular cortical area (58, 230).

The various types of immediate responses obtained will now be described.

'ACTIVATION' OR 'AROUSAL' RESPONSE. As first reported by Sloan & Jasper in 1950 (231), high-frequency electrical stimulation of the anterior cingulate cortex in cats anesthetized with diallyl barbituric acid may produce a 'desynchronization' of the electrocortical activity of all cortical regions similar to the EEG arousal following stimulation of the brain-stem reticular system and peripheral sensory nerves. The most prominent feature of the response is the disappearance of the intermittent 6-to-12-per-sec. bursts or spindles and their replacement by a high-frequency low-voltage activity. The same effects were elicited by Kaada (126) on exciting the anterior cingulate, subcallosal, orbitoinsulotemporal polar cortex, the olfactory pathways and amygdala in cats, monkeys and chimpanzee (the dotted areas shown in fig. 2). A typical example is given in figure 8. In nonanesthetized animals the EEG responses from these areas appear to be allied to the behavioral arousal induced from the same regions (134; Fangel & Kaada and Kaada & Johannessen, unpublished observations). These findings have recently been confirmed in the monkey (225) and, for the anterior cingulate, in man (233). The same type of EEG response has also been elicited from the cortical regions on the lateral aspect of the hemisphere stimulation of which causes, as described above, similar behavioral arousal in unanesthetized

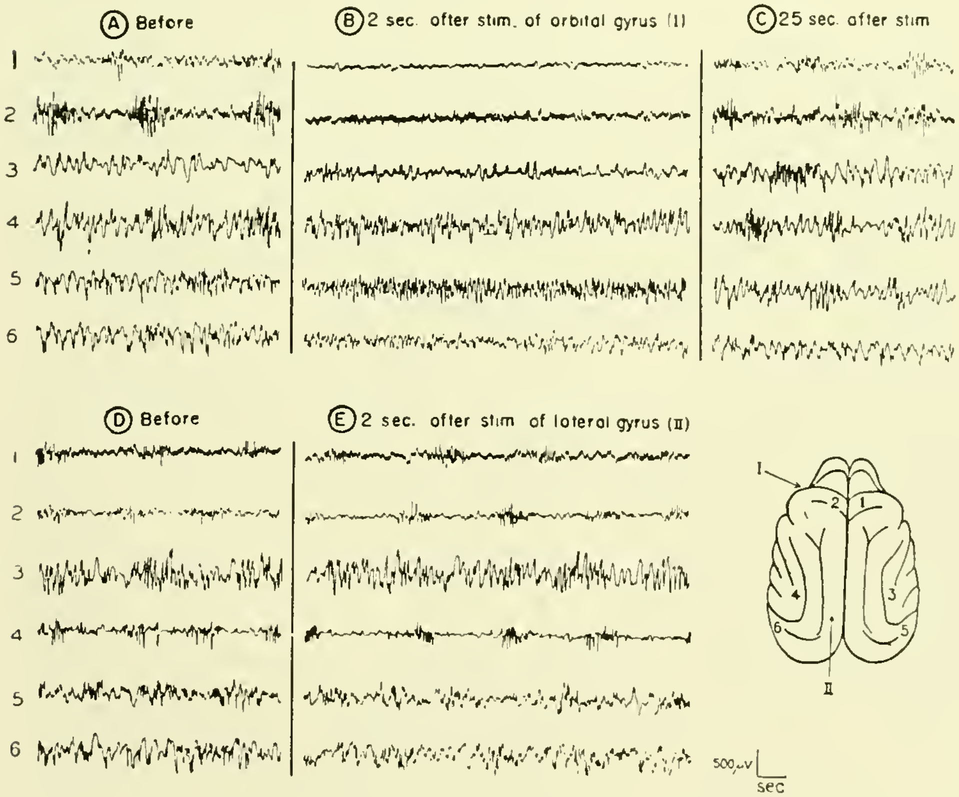

FIG. 8. Generalized 'arousal' of the EEG on stimulation of the left orbital gyrus of the cat for 3 sec. (at *arrow I*). *A:* Control. *B:* Disappearance of intermittent burst potentials with increased frequency of cortical potentials. *C:* Return to normal after 25 sec. *D* and *E:* Stimulation of the left lateral gyrus at *arrow II* with the same stimulus parameters failed to produce any effect at the six cortical electrodes. [From Kaada (126).]

animals, namely the intermediate frontal cortex, parts of the sensory-motor cortex, superior temporal gyrus and paraoccipital region (225). The cortical points from which Bremer & Terzuolo (31, 32) evoked identical EEG effects appear likewise to be located within these zones. The cortically induced EEG arousal is readily blocked by anesthetic agents (225; Kaada & Johannessen, unpublished observations). Even in lightly anesthetized animals the effect is rather inconstant and the regions influenced are more or less restricted. The most effective loci are found in the cingulate and temporal polar cortex and in the superior temporal gyrus (225; Kaada & Johannessen, unpublished observations). This is consistent with the finding that these cortical areas are also more effective in inhibiting spontaneous movements (as part of the arousal response) than the frontal, parietal and occipital inhibitory fields (126).

The cortically induced EEG arousal is not secondary to accompanying respiratory or arterial pressure alterations (126). It may further be associated with either facilitation, inhibition or no effect of movements evoked from the motor cortex (126, 232). The response depends on a cortical-subcortical mechanism (126, 231) and, like the behavioral arousal, it is most likely produced via the brain-stem and thalamic reticular system (126, p. 238; 231). The cortically evoked EEG arousal is present in the *encéphale isolé* (31, 32, 126). The primary and secondary components of cortical potentials evoked by sensory stimulation are unaffected during cortically induced EEG arousal, whereas the subsequent 'evoked burst potentials' are blocked (126).

BURST AUGMENTATION. Occasionally stimulation of points in the anterior cingulate (126, 231), orbital and rostral pyriform cortex and in the olfactory tubercle (126) in animals under light barbiturate narcosis may result in an increase in the burst prominence in all cortical areas. The response, which appears to be opposite of that characterizing the EEG arousal, is probably mediated via the thalamic reticular system which is the only subcortical structure at present known to initiate generalized bursts on stimulation.

ELECTRICAL AFTER-DISCHARGES. A characteristic feature of the anterior cingulate, subcallosal and orbito-insulotemporal polar cortex, as well as of the amygdala and hippocampus, is a low threshold for elicitation of seizure discharges as compared to that of neocortical areas. This was first shown by Gibbs & Gibbs (90) for motor seizures and by Jung (124), Lennox *et al.* (152) and Kaada (126) for electrical after-discharges from the hippocampus, amygdaloid region and medial-basal cortical areas, respectively. These findings have later been confirmed by a number of investigators (12, 48, 79, 83, 95, 96, 125, 126, 154, 155, 193, 208). The lowest threshold for electrical after-discharges is found in the hippocampus, amygdala and pyriform cortex. Details about the various types and preferential pathways of spread are found in the papers just referred to. Of particular interest is the observation that after-discharges elicited from almost any of the areas concerned readily spread into the others, suggesting a close functional relationship between them (12, 48, 126), as also demonstrated by physiological neuronography (192, 203). Mention should further be made of the generalized petit mal-like 3-per-sec. spike and wave formations associated with clinical manifestations of petit mal epilepsy which have been evoked from the anterior cingulate cortex in animals (126, 153, 193).

The vast literature on the relation of psychomotor seizures or automatism to the temporoinsular region is reviewed elsewhere (65, 84, 127, 168, 187) and will not be discussed further in this connection. Brief mention should only be made of the immediate 'flattening' (also termed 'suppression') of electrical activity, including spikes, at the onset of the seizure in the majority of patients with temporal automatism (66, 88, 109, 121, 123, 171). Such 'suppression' may be generalized, bitemporal or unilateral. This phenomenon, together with the clinical features of automatism, can be reproduced in man at operation by stimulation of the anterior temporal-insular gray matter and the region of the claustroamygdaloid complex and anterior hippocampus (65, 66, 123). Similar effects have been produced from the homologous areas in cats (85, 126) and monkeys (50, 126). It seems likely that the effect is identical with the 'activation' response (126, 127).

OTHER ELECTROCORTICOGRAPHIC EFFECTS. Various other types of effect in the EEG in response to stimulation of the areas under discussion have been described as 'suppression' or 'elimination of strychnine and unelicited spikes' (59, 152), 'suppression of spindles' (59), 'attenuation' (231) and 'depression' (126) of electrocortical activity. The functional significance of all these types of effect is not clear. Experimental evidence has been given that the 'attenuation' response and the 'suppression of spindles,' without any appreciable increase of frequency of the

background activity, actually represent an abortive arousal effect (126, p. 207). Further, the 'depression' and 'elimination of strychnine and unelicited spikes' mainly represent unspecific extinction phenomena which can be obtained from any cortical area (126, p. 231 and 244).

EFFECTS OF ABLATION

No conclusion concerning the functional significance of a particular portion of the brain can be drawn solely on the basis of stimulation experiments. A better understanding is reached by comparing the results of stimulation and ablation. In the past 5 to 10 years a considerable amount of data on ablation of the cortical areas under discussion has accumulated. Important contributions have come also from clinical studies in connection with surgical intervention of these portions of the brain in psychiatric and epileptic patients. Only clinical papers which may contribute to an understanding of the functional role of the area concerned will be mentioned.

An important conclusion which has emerged from all ablation studies, in animals and man, is that neither unilateral nor bilateral lesions of the cingulate and orbitoinsulotemporal polar region interfere with the correct integration of basic elementary somatomotor and autonomic mechanisms (with the exceptions mentioned below), nor with functions essential for survival. Thus, there has been no change in voluntary or reflex motor performance, no muscular hyper- or hyporeflexia, no disturbance of respiratory, cardiovascular and gastrointestinal functions, no pupillary change, etc. This in spite of the fact that the same areas, on stimulation, are able to exert a profound influence upon these very same functions probably as a part of more complex behavior patterns. This influence on basic autonomic and somatic mechanisms therefore is probably not of a tonic character.

Some exceptions to these essentially negative results are the slight elevation of skin temperature of the extremities and the augmentation of reflex vasodilation on exposure to a warm environment following bilateral removal of the posterior orbital surface in monkeys (54, 159). More recently, Showers & Crosby (227) have recorded a transitory drop in body temperature (average 5.5°F = 3°C) in monkeys with lesions of the posterior or anterior cingulate cortex. Also, it was possible to observe piloerection and an increase in sudomotor activity in the 2 to 3 weeks following the operation. Further, Babkin & Kite (15) found that bilateral ablation of the cingulate gyrus in acute experiments in dogs produced a moderate increase in the rate of contractions of the pyloric antrum, whereas orbital surface ablations were without significant effects. Finally, Turner (256) has shown that removal of the posterior orbital cortex in monkeys results in increased resistance to anoxia, possibly because ". . . a protective mechanism had been damaged or destroyed." Davis (52) observed that monkeys with bilateral ablation of area 13 quickly collapse when exposed to an altitude equivalent of 20,000 ft., while normal unoperated animals are able to maintain normal activity at this altitude for 30 min. or longer.

The more prominent changes which ensue after bilateral lesion of the cingulate and orbitoinsulotemporal cortex are all concerned with the behavior of the animal, such as increased motor restlessness and changes in the affective state of the animal. But also in these respects the changes are not very striking and bilateral removal is necessary to obtain any significant effects.

Anterior Cingular Region

Bilateral anterior cingulate ablation in monkeys by Smith (236) and Ward (266) has resulted in behavior changes in the direction of greater tameness and diminution of preoperative fear and rage in response to man and in lack of 'social consciousness' (Ward). This was confirmed in a general way by Glees *et al.* (91) but they report that the behavior changes were rather short-lived, disappearing after 6 wk. to 3 mos. Pribram & Fulton (201) and Mirsky *et al.* (178) recently reported that in monkeys resection of the cortex of the anterior cingulate gyrus, and of the pre- and subcallosal and medial frontal areas as well, does not lead to any profound and prolonged alteration in behavior in response to other animals; the effects are transient, apparently minimal and difficult to appraise. However, cingulectomy may have the effect of making monkeys temporarily more aggressive or less fearful of man (178). Bard (26) found that bilateral lesion of the cingulate cortex of cats does not per se alter the threshold at which rage provoking stimuli become effective. Further, Rothfield & Harman (212) concluded that removal of the neocortex plus cingulate cortex in cats does not alter the rage threshold. Some increased motor restlessness, similar to but less than that resulting from posterior orbital ablation (see below), has been observed following

bilateral anterior cingulate removal in monkeys (91, 266).

Using rats with bilateral lesions in the area of the anterior cingulate gyrus, Peretz (191), quite recently, has shown that they took significantly longer than normal animals to learn an avoidance response when motivated by fear of electric shock. This latter experiment included a series of control procedures which indicated that the results could probably not be accounted for in terms of lessened sensitivity to electric shock, general reduction of all motivation or intellectual deficit.

The earlier observations that apprehensiveness and anxiety seem to disappear after cingulate ablations have led several neurosurgeons to remove this region in agitated, aggressive and overactive psychotic patients and in anxiety and obsessional states (28, 138, 149–151, 157, 219, 251, 253, 267, 273, 274). According to the earlier as well as to subsequent reports the results appear promising when the procedure is applied to carefully selected cases. No intellectual impairment has been reported to follow such ablation (75, 126, 150, 206).

After bilateral cingulate ablations in the cat Kennard (137) has recently observed confused, perseverative, obsessive behavior, a plasticity of posture and a slight increase in rage reactions. It is stated that in these cingulate ablations the only area removed was that lying in the region called area 24 in monkey and man. It appears from the illustration, however, that the ablations have mainly included the posterior granular subdivision of primates, area 23 or the 'cingular area' (*Cg.* in fig. 7*E*) in Rose & Woolsey's terminology (209), whereas the area corresponding to the agranular anterior cingulate cortex of primates (area *La.* in fig. 7*E*) was spared in most animals. Kennard's syndrome, which in many respects resembles that seen in destructive lesions involving the cingulate gyrus in man (7, 8, 28), may perhaps be due to a lesion of the granular posterior cingulate cortex. It should be emphasized that in the cat as well as in primates the most profound autonomic and somatomotor effects of stimulation are elicited from the pre- and subcallosal region of the cingulate cortex.

Posterior Orbital Cortex

The most marked behavior change which follows ablation of this region in monkeys is motor restlessness (71, 159, 213). According to Ruch & Shenkin (213), this hyperactivity appears to be a fairly specific phenomenon, manifested chiefly in locomotion, whereas other motor activities, such as expressivity, were rather reduced in variety and quantity. The hyperactivity possibly represents a release phenomenon, consequent on removal of the inhibitory influence on somatic movements exerted by the posterior orbital cortex, as well as by other areas ablation of which yields motor hyperactivity (126, p. 249). These changes in spontaneous motor activity have not followed similar posterior orbital lesions in man (218, 222). According to Davis (52) and Turner (256), the hyperactivity in monkeys after posterior orbital ablation is profound only if the subjacent head of the caudate nucleus has been damaged.

In line with these observations in monkeys Dax & Radley-Smith (53) emphasized that in performing frontal leucotomy in man the lower and posterior sections should be avoided in very excited and restless patients. Orbital undercutting or orbital ablation has been recommended for depressions and catatonic stupors with subnormal psychomotor activity [see (75) for references]. A number of other clinical papers deal with these problems (68, 69, 72, 174, 175, 196, 214, 218, 221, 222, 252).

Anterior Temporal Region

Unilateral anterior temporal resections in animals and man apparently cause no appreciable defects as shown, for instance, by the several hundred such ablations which have been carried out in epileptics for the relief of psychomotor seizures (17, 19, 20, 64, 89, 177, 181, 186, 189). On the other hand, bilateral removal of the anterior portion of the temporal lobe in primates and of the homologous areas in subprimates causes profound changes in behavior. On several points, however, the various reports are somewhat contradictory. The effects of bilateral removal of the temporal lobes, including most of the uncus, amygdala and hippocampus in monkeys, were described by Klüver & Bucy in 1937 (141) as "the most striking behavior changes ever produced in animals." These behavior changes consisted of *a*) 'psychic blindness' or 'visual agnosia'; *b*) 'hypermetamorphosis' or excessive tendency to examine objects visually, tactually and orally; *c*) a remarkable decrease of aggressive behavior and loss of fear reactions; *d*) bizarre sexual behavior; and *e*) considerable changes in dietary habits (139, 142, 143). On the other hand, Bard & Mountcastle (27) demonstrated that bilateral removal of apparently the same structures in cats, particularly of the amygdala and of much of the pyriform cortex, produced savageness and a considerable increase in

rage reactions. The different effects obtained in these two studies were considered to be due to species differences. This explanation is not entirely compatible with the somewhat 'paradoxical' results obtained by Spiegel *et al.* (242) who observed both rage reactions and cataleptic symptoms following bilateral lesions of the amygdaloid region in one and the same species of animal (cats). Docile cats as a result of such lesions have also been reported by Schreiner & Kling (217) and Brady *et al.* (30). It seems more likely that the structures removed are not completely analogous in all these experiments. Lesions of the anterior portion of the temporal lobe may include in varying degrees such diverse structures as the pre- and periamygdaloid cortex, the entorhinal area, juxtallocortical and neocortical zones or their efferent or afferent projections, olfactory pathways, the amygdaloid nuclear complex (with its at least six subdivisions with different projections), and more or less the temporal portion of the hippocampus proper. Apparently, our "present knowledge and techniques do not permit sufficiently accurate pinpointing of crucial structures" (197, p. 59).

The results of Klüver & Bucy (143) and more recent ones (180, 248) ascribe more importance to the medial temporal structures than to the lateral temporal cortex. Various manifestations of the Klüver-Bucy syndrome have been reproduced in monkeys (179, 183, 200, 248), cat (30, 217) and man, where it includes memory loss (97, 216, 220, 247) when the bilateral lesions are mainly restricted to the anteroventral portion of the temporal lobe. It is not clear, however, which basic functions have been disturbed by the various lesions. Recent attempts to analyze the complex syndrome associated with large bitemporal lesions through the use of a battery of behavioral observations and tests and more rigidly controllable techniques of experimental psychology seem promising (30, 179, 180, 200). According to Pribram & Bagshaw (200), such measures have related the posterior orbital surface to locomotor activity, the anterior insula to taste, and the temporal polar and amygdaloid region to food intake, temperature regulation and 'hypermetamorphotic' behavior. Visual discrimination ability is unaffected either by such lesions (200) or by hippocampectomy but depends on the integrity of the medial occipitotemporal region (43, 179, 180).

It is still a matter of controversy exactly which lesions are responsible for increased rage reactions. Lesions of the basal structures just rostral to the optic chiasma (77, 78), the olfactory tubercles (242), amygdala (27, 242), or the hippocampal-fornix system in cats with absent neocortex (212) have all lowered the rage threshold. However, either no effects or opposite effects, such as increased tameness and docility, have been observed after bilateral lesions of the amygdaloid complex (9, 30, 212, 217, 242, 275), the hippocampus-fornix (26, 27, 212, 272) or the junction of the tail of the caudate and putamen (256). None of the increased rage responses produced after cortical, amygdaloid or hippocampal lesions, however, is comparable to the savage behavior of extreme type which follows lesions of the ventromedial hypothalamic nucleus (272).

Further consideration of behavioral changes following temporal lesions are found in the two succeeding chapters on the hippocampus and amygdala.

PHYSIOLOGICAL SIGNIFICANCE

Olfaction

It appears at present widely accepted that only more restricted anterior basal areas of Broca's *grand lobe limbique* (a portion of the pyriform cortex together with parts of the amygdala, olfactory tubercle, bed nucleus of the stria terminalis and other regions) are implicated in important olfactory functions. This applies both to the detection and discrimination of olfactory impressions and to olfactory reflexes and associated feeding reactions (2, 36, 37, 176, 202). (Chapter XXI by Adey in this *Handbook* is devoted to this topic.) The functional terms 'olfactory brain' and 'rhinencephalon' therefore should not be used in the wider sense as identical with the 'limbic lobe' because these terms suggest that there is a particular function common to all formations included in this portion of the brain, an assumption which is not supported by experimental evidence. The main functions of the other parts of the 'limbic lobe' must be sought in other spheres of activity.

Visceral Functions

In spite of the extensive physiological, anatomical and clinical data that have accumulated in the past decade nothing conclusive can as yet be said about the functional significance of these other formations of the 'limbic lobe.' It has recently become customary to speak of the 'visceral brain' (10, 162, 163, 165, 197) as synonymous with the 'limbic lobe,' thus imputing to this entire brain area another specific common function. However, thus far all of the experimental

data have confined the areas of the 'limbic lobe' which influence autonomic activities to a rather limited portion of its rostral part, comprising the anterior cingulate, orbitoinsulotemporal polar region and the amygdala. There is at present no evidence, either from stimulation or from ablation experiments, to justify the application of this term to the posterior portions of the cingulate and hippocampal gyri or to the hippocampus-fornix system (126, 202). Further, the rich variety of autonomic and somatomotor responses evoked from the rostral allo- and juxtallocortical areas and amygdala are all independent of the hippocampus-fornix (126). Even if the term 'visceral brain' is confined to these rostral mediobasal areas it becomes somewhat misleading since somatic responses from the same areas appear to be just as prominent as the visceral ones.

Emotion

Two decades have passed since Papez (184) proposed the now famous and much quoted theory that the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnections possibly constitute the central anatomical substrate for emotion. This hypothesis seemed to find support in the emotional changes resulting from Klüver & Bucy's (141–143) temporal and Smith's (238) and Ward's (266) anterior cingulate ablations in monkeys. The more recent temporal ablations, referred to above, tend to relate the changes in emotional behavior to lesions in the amygdaloid region rather than to the more posterior temporal cortex and hippocampus. Further, as regards the anterior cingulate region, renewed studies find as yet no conclusive evidence to substantiate the earlier claims of the importance of this area in emotion. One might also question whether the anterior cingulate area actually represents an essential integrative part of the postulated hippocampal-cingulate 'circuit,' since in the phylogenetic scale the anteromedial thalamic nucleus (projecting upon the anterior cingulate area) is considerably reduced (226, 250) whereas the anteroventral nucleus, which in higher mammals receives the bulk of fibers from the mammillary bodies, shows a progressive development similar to that of the hippocampus, fornix, mammillary bodies, mammillothalamic tract and most of the cingulate gyrus (211). These phylogenetic data together with the essentially negative results of stimulation and ablation in animals might indicate, as previously suggested (126, p. 258), that these structures are concerned in higher psychic functions rather than in physiological activities of a primitive elementary type. Data are at present accumulating which tend to show that the hippocampal-cingulate system possibly might be critically concerned in memory function (122). Whether these structures, or parts of them, are in any way primarily involved in emotional behavior can be resolved only in future experiments. Potentials have been recorded by several authors from the pyriform cortex, amygdala, hippocampus and cingulate gyrus in response to various types of sensory stimulation (visceral, auditory, visual, olfactory, gustatory and somatic). It has been suggested that these latter potentials are possibly related to emotional experience (164). There are, however, at present several discrepancies in the findings of the various authors and more information is needed before anything can be said about the functional significance of these sensory impulses.

More recently Turner (255, 256) has introduced the term 'thymencephalon' for much the same structures as contained in the 'rhinencephalon,' 'limbic lobe' or 'visceral brain' in order to denote the affective or temperamental part of the brain (*thymos*: mind, spirit, soul, passion). However, of all the structures included in these terms only the amygdala and the orbitoinsulotemporal polar cortex and possibly the subcallosal and septal regions appear to be related to emotional behavior (202). (Emotion is considered in Chapter LXIII by Brady in this *Handbook*.)

'Attention' or 'Arousal' Response

The significance of the behavioral and EEG-'arousal' or 'attention' response which rather extensive parts of the cingulate and orbitoinsulotemporal polar regions and part of the amygdala and hippocampus share with neocortical areas—is not clear. Although these diverse cortical zones seem to have some common functions related to the arousal response, it is extremely unlikely, as also emphasized by French *et al.* (70), that all influences mediated by them are identical or that these are the only functions they subserve. It appears likely that alertness associated with functional activity of the different cortical areas may be related to different patterns of general behavior. In this respect, it should be mentioned that if subsequent findings indicate that the medial-basal cortical areas in some way are concerned with emotional behavior, it would be extremely reasonable to find 'arousal' responses elicited from these as well.

It may also be of significance that most of the corti-

cal 'arousal' areas (olfactory, acoustic, visual, somatosensory, splanchnic and vagal) are located in the immediate vicinity of sensory projection areas and further that they all, on stimulation, appear to yield contraversive searching movements, possibly of an orienting character.

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The hippocampus

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CHAPTER CONTENTS

CONNECTIONS OF THE HIPPOCAMPUS

Terminology

The hippocampus has attracted the attention of anatomists since Thomas Henry Huxley and Bishop Wilberforce disputed its evolutionary significance, and Charles Kingsley parodied them in *The Water Babies*. Many anatomists have studied this functionally enigmatic part of the brain, and in the confusion many terminological disagreements have occurred. The general location and contours of this region in man are shown in figure 1. Figure 2 shows many of the gross anatomical features and some of the connections of the hippocampus of the cat. To some, hippocampus means the hippocampal gyrus, and to others the archicortex which is folded into the lateral ventricle. The latter sense is used here. Entorhinal cortex and pyriform cortex will be used interchangeably to mean the cortex lying on the ventral aspect of the temporal lobe medial to the rhinal fissure. The junctional region between the entorhinal cortex and the hippocampus, lying on the medial aspect of the temporal lobe beneath the choroidal fissure, is called the subiculum. The single-layered cortex which is enfolded into the lateral ventricle is subdivisible into two interlocking gyri formed by the hippocampal pyramids and gyrus dentatus. Here it is collectively called Ammon's horn or hippocampus. The term hippocampal gyrus will be avoided since most American and British authors consider entorhinal cortex and hippocampal gyrus to be more or less identical. By hippocampal formation is understood Ammon's horn (hippocampus plus gyrus dentatus) with its adjacent and continuous regions of the brain, and its chief afferent and efferent pathways. Grossly, these structures include the subiculum and entorhinal cortex, the gyrus cinguli and amygdala, the psalterium (hippocampal commissure), the septum lucidum and the fornix. It also includes certain embryological rudiments, the striae longitudinales and the indusium griseum. The fornix is considered to comprise, first, the postcommissural fornix extending to the mammillary body, second, the precommissural fornix which connects the hippocampus and the septum (within which lies the related diagonal band of Broca and radiation of Zuckerkandl) and, third, the dorsal fornix, by which is meant the band of white fibers extending rostrally above the septum lucidum and beneath the corpus callosum, and grossly traceable caudally toward or into the colonne horizontale of Gerebtzoff (39) or 'spheno-cornual' bundle of Ramón y Cajal (90). The term dorsal hippocampus is used to imply the dorsal subcallosal hippocampus seen in many mammals, and the dorsal supracallosal hippocampus will be referred to as the indusium griseum (gray matter) and striae longitudinales (white).

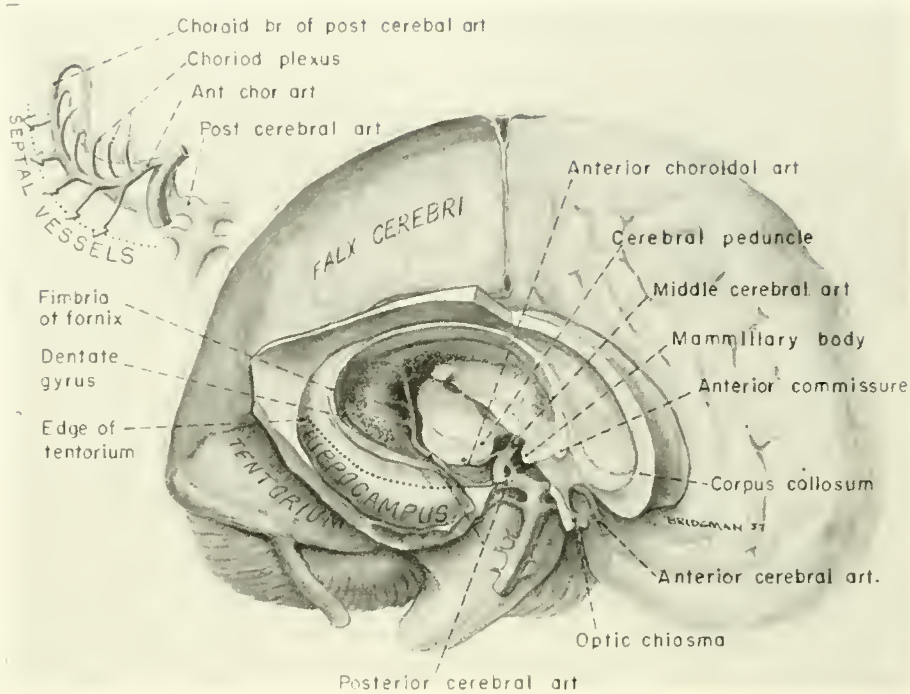

FIG. 1. Drawing of a dissected human hippocampus. The hemisphere has been partially removed, the midbrain is cut across and the third ventricle exposed. The *dotted line* represents the edge of the tentorium which, as shown in the diagrammatic insert, crosses at right angles to the vessels which supply the hippocampus. In cases of temporal herniation they may be occluded.

Phylogeny

The hippocampal primordium (which becomes Ammon's horn) and the piriform cortex comprise the bulk of the cerebral hemisphere in amphibians and other lower vertebrates. Only in amphioxus is the hippocampal primordium, together with the rest of the cerebral hemisphere, wanting. Thus, the hippocampal primordium and piriform cortex are the cerebral hemisphere of primitive vertebrates and perform whatever cortical functions are within the capabilities of these animals.

The neocortex develops between the piriform cortex and the hippocampal primordium and, consequently, distorts the cerebral hemisphere. This process is exaggerated by the growth of the interhemispheric commissures. Of the four commissures, three are found in the anterior wall of the developing neural tube in front of the interventricular foramen of Monro: the anterior commissure, the hippocampal commissure, or psalterium, and the corpus callosum. A fourth, the posterior commissure, lies caudally and dorsally to the foramen of Monro. According to Johnston (57), the anterior commissure lies just below the remnant of the anterior neuropore (fossa triangularis) and thus marks the rostral extremity of the primitive neural tube. The anterior and posterior commissures are not greatly modified by the development of the forebrain, nor do they modify the relationships of the hippocampal primordium. The development of the corpus callosum, on the other hand, between the two neocortices, leads to considerable change in relationships.

Much of our knowledge of the formation of the hippocampus, as it exists in mammals, is due to Elliot Smith (102–105). He regarded the primitive hippocampus as being entirely supracallosal in position and accounted for the large infracallosal hippocampus (the dorsal hippocampus of our terminology) as the result of the formation of the 'hippocampal flexure,' caudal to the splenium of the corpus callosum. Such a concept leads to some difficulties in interpreting the way in which the hippocampal commissure comes to lie infracallosally and yet remains in contact with the hippocampus proper which in primates is pushed backward because of the growth of the corpus callosum and eventually comes to lie almost entirely in the temporal lobe. The difficulty is largely resolved by Johnston's (56–58) concept that the septum, fornix and hippocampal commissure represent part of the paraterminal body, a forward and anterior extension of the hippocampal primordium lying in front of the lamina terminalis. The paraterminal body may be considered to be functionally related to the hippocampal primordium, regardless of where the exact boundary between the two exists. Such a concept makes the various relationships of the hippo-

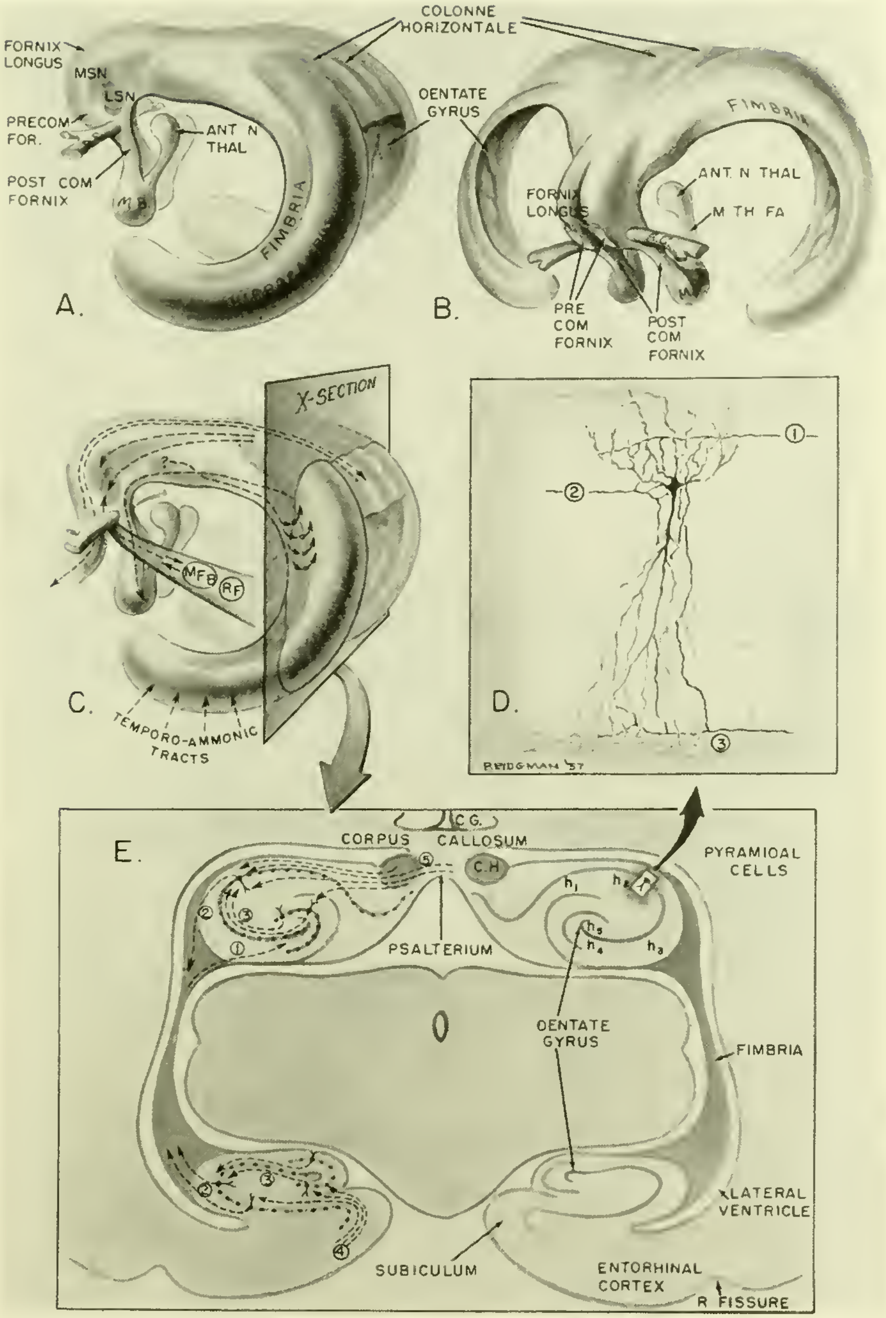

FIG. 2. Diagrams of the hippocampus of the cat. *A:* Drawing of dissection from the left side. *B:* Same from the front. *C:* Same as *A* but showing some of the conduction paths; *MFB*, median forebrain bundle; *RF*, reticular formation. *D:* Termination of afferents about a hippocampal pyramid: *1*) from the alveus, *2*) from dentate granule cells and *3*) from the temporoammonic tract. *E:* Schematic cross section at level shown in *C*, showing *1*) afferents from the fimbria to the dentate gyrus, *2*) axons of pyramidal cells, *3*) dentatopyramidal fibers, *4*) temporoammonic fibers and *5*) fibers from *colonne horizontale* and psalterium; h_1 to h_5 show the approximate locations of pyramidal neuron fields. The rudimentary supracallosal hippocampus is omitted for simplicity.

campus in different species easy to understand. The corpus callosum, then, is conceived to grow through the hippocampal primordium-paraterminal body; in this way, fibers to and from the hippocampus can be found above and below the corpus callosum and also incorporated within it. As a result of this growth of the corpus callosum and the burgeoning of the cerebral hemispheres, the hippocampus gradually retreats into the temporal lobe.

General Anatomy

The primitive position of the hippocampal primordium helps to explain the afferent and efferent connections of Ammon's horn. Before the development of the neocortex, the hippocampus establishes connections with the brain stem. These connections are made through the region of the paraterminal body to the hypothalamic and other diencephalic areas, as well as toward the striatum. Thus, Herrick

(54) was led to conclude that the hippocampal primordium served to correlate afferent impulses from a variety of brain-stem visceral centers and to relay them secondarily to the neocortex. The commissural systems, developing late, distort the secondary connections less than they distort the primary, and the connections we see in mammals of this type are chiefly the fibers of the temporoammonic tract (3, 4, 72, 73, 90, 91). The septum lucidum may be considered to be the main remnant of the paraterminal body. It follows, therefore, that the brain-stem connections to and from Ammon's horn enter through the septum lucidum among the fibers of the fornix system. The connections between the mammillary body and anterior thalamus (tract of Vicq d'Azyr) is also phylogenetically new and probably is to be associated with the further development of hippocamponeocortical connections.

The system of fibers which comprise the fornix and psalterium may be considered, perhaps, without immediate reference to the exact direction of the axons within them. In an animal like the cat, when the upper part of the cerebral hemisphere and corpus callosum is removed so that the hippocampus may be observed from above (as the floor of the lateral ventricle), two prominent bands of white matter (the fimbriae) are seen converging rostrally to lie above the septum lucidum (see fig. 2). Lateral to these bands lie the choroidal fissure and the caudate nuclei. Medially to them lie the dorsal hippocampi which are separated by a band of white matter composed of dorsally running longitudinal fibers and more ventrally placed transverse fibers. The longitudinal fibers which lie between the hippocampi may be seen to consist of two parallel bands which extend forward to blend with the fimbria as it becomes the dorsal fornix above the septum lucidum. These are the *colonnes horizontales*. The deeper-lying transverse fibers are the fibers of the psalterium.

The bulk of the fibers of the fimbria do not join the dorsal fornix but instead diverge in two bundles: *a*) a compact bundle which dives deeply behind the anterior commissure to pass through the hypothalamus and eventually reach the mammillary body, the postcommissural fornix, and *b*) a looser group of fibers, the precommissural fornix, entering the septum and passing in front of the anterior commissure. The postcommissural fornix is probably almost exclusively efferent (22). The precommissural fornix and dorsal fornix are probably both afferent and efferent, the latter being chiefly related to field h_1 (30, 52). According to Gerebtzoff (39), the *colonne horizontale* contains fibers afferent to the hippocampus from the septum. The hippocampal commissure, presumably, contains afferent and efferent fibers between the two adjacent Ammon's horns, but it is possible that its rostral part also contains fibers which cross to the contralateral septum. Grossly, three general areas of the hippocampal commissure may be recognized: a fairly thick caudal bundle which is more or less blended with the splenium of the corpus callosum; a thinner middle segment consisting of string-like fibers passing between the two hippocampi, giving rise to the fanciful name of psalterium (a harp); and, again, a large commissural mass at the rostral end of the hippocampus connecting the two fornices.

Besides the classic studies of Ramón y Cajal (90, 91) and Elliot Smith (102–106), the reader interested in afferent and efferent connections of the fornix and the hippocampal commissure is referred to recent papers by Nauta (82), Blackstad (17), Simpson (101), Daitz & Powell (30), Powell & Cowan (86–88), Cowan & Powell (28), Gerebtzoff (39), Morin (79), Allen (12), Sprague & Meyer (107), Guillery (52), Fox (34, 35), and the review of Pribram & Kruger (89). Figure 3, constructed on the basis of the electrophysiological studies of Green & Adey (45) shows brain areas affecting and affected by hippocampal activity.

Projections

CORTEX. Connections with the cortex, as indicated above, are established through the temporoammonic tracts. They connect the entorhinal cortex to Ammon's horn, both via the gyrus dentatus and the hippocampus itself. Ramón y Cajal (90) described the spheno-occipital ganglion as the source of origin of the axons of the temporoammonic tract. This is a specialized part of the entorhinal cortex, particularly prominent in smaller mammals, from which these fibers seem to rise but it is not strictly delimited. Although experimental stimulation of the hippocampus (2, 5, 45, 51) indicates that evoked potentials can be obtained from the entorhinal cortex, so far the anatomical pathways which might subserve these connections have not been detected. Functional studies by Adey *et al.* (5) in the Australian phalanger, a marsupial, showed that stimulation of the entorhinal cortex evoked responses in the hippocampus but only small and irregular responses in the fornix despite the large responses which could be evoked in the hippocampus by stimulating the fornix. [See also the studies of Green & Morin (50) in the guinea pig.] They believe that the dorsal hippocampus can exert a powerful

FIG. 3. Schema of areas apparently receiving impulses from or distributing impulses to the hippocampus. On the *left side* of each brain section *vertical hatching* marks areas which when stimulated evoke responses in the hippocampus which are always bilateral. On the *right side* of each section, *crosshatched areas* are those bilaterally excited by stimulation of the hippocampus. *Stippled areas* are ipsilaterally excited by hippocampal stimulation. [From Green & Adey (45).]

effect on the entorhinal area on the basis of interaction studies. In a second paper Adey *et al.* (1) reported the use of electrophysiological techniques to trace a pathway from the entorhinal cortex caudally through the thalamus to the periaqueductal gray and dorsal tegmentum.

The gyrus cinguli presumably projects to the hippocampus in a fashion similar to the entorhinal cortex, establishing axodendritic synapses with the pyramidal and granule cells. It is also possible that more or less direct connections are established from the gyrus cinguli to the hippocampus through the fibrae perforantes corpus callosi, groups of fibers which have been described from time to time as penetrating the corpus callosum (64).

THALAMUS. Thalamic connections of the hippocampus are not well understood. Direct connections between the hippocampus and the thalamus are probably present. They were claimed by some of the older anatomists and have recently been traced by the bouton degeneration technique (52, 82). Green & Adey (45) found short latency responses in the anterior thalamus following hippocampal stimulation

but could not determine that they were due to direct connections. On the other hand, secondary connections, via the mammillary body, are well established (27, 33, 43, 82, 87, 111), and there is evidence for connections to the anteromedial, anterodorsal and anteroventral nuclei, as well as to the intralaminar nuclei (45). Rose & Woolsey (94 96) demonstrated the relationship between rostral thalamus, cingulum and rhinencephalon, and found that removal of the rhinencephalon, striatum and amygdala led to degeneration of the mid-line and intralaminar nuclei of the thalamus. Powell (85) reported a case of complete surgical hemidecortication in which, however, the mid-line and intralaminar nuclei, as well as the nucleus limitans and the parafascicular nucleus, showed no evidence of any change 24 days postoperatively, but the anterior nuclei showed extreme degeneration. The fornix was apparently spared. The anterior nuclei of the thalamus (particularly the anteromedial and anteroventral) are thus functionally related to the hippocampus, and there also may be connections, perhaps secondarily, with intralaminar nuclei and mid-line nuclei. Stimulation of the hippocampus evokes responses in the anterior, mid-line and intralaminar nuclei, and stimulation of these nuclei evokes recruiting responses in the hippocampus itself as well as in the neocortex. In the guinea pig, stimulation of the precommissural fornix (50) also leads to recruiting responses.

OTHER AREAS. Direct connections to the mammillary body are well known. The main region of termination is the medial mammillary nucleus (30, 52). Connections with other parts of the hypothalamus, besides the mammillary body, are not certain although there seems to be a good deal of evidence that a few fibers of the fornix leave it before it reaches the mammillary region. Some fibers probably continue from the fornix directly into the tegmentum where Nauta (82) and Guillery (52) have seen bouton degeneration, and Green & Adey (45) have found short-latency responses in a zone between the red nucleus and the substantia nigra.

There are numerous and important connections in the septal area. Many of these are efferent, particularly to the medial septal nuclei; but in this region there is a vast convergence of fibers extremely difficult to unravel. Ramón y Cajal's (90) views on the structure and connections of the septum lucidum and on its relationship to the hippocampus are given in detail in a recent translation. It seems unlikely that very much more may be added by direct anatomical studies on normal material. Daitz & Powell (30) found that division of the fimbria resulted in complete atrophy, or shrinkage, of the cells of the ipsilateral medial septal nucleus and partial degeneration of the nucleus of the diagonal band, but that additional involvement of the fornix or stria terminalis, that is to say the dorsal portions of the fornix, did not result in any intensification of this degeneration. Nor did they find that degeneration occurred in the septum following destruction of the entorhinal cortex or amygdala. Powell & Cowan (88) found that division of the dorsal fornix and fimbria results in complete atrophy of the descending column of the fornix, but that lesions of the fimbria resulted in only slight degeneration of the descending column of the fornix although there was a complete loss of precommissural fibers in the septum and degeneration of the medial cortical hypothalamic tract. They concluded that most of the efferent fibers of the fimbria ended in the hypothalamus anterior to the mammillary nuclei. They believed that the axons of the pyramidal cells of field h_1, which would be the medial field of pyramidal cells in a section through the dorsal hippocampus, turn medially in the alveus into the dorsal fornix, while those of cells in fields h_2 and h_3, or laterally placed cells, have axons which bend laterally toward the fimbria. Thus, they conceived that the lateral portions of the hippocampus project chiefly to the septum and hypothalamus, whereas the medial portions project toward the mammillary body.

Although the physiological evidence for afferents to the hippocampus from the septum seems indisputable, the precise anatomical pathways concerned are as yet by no means clear. Gerebtzoff (39) found Marchi degeneration extending backward in the *colonne horizontale* following lesions in the septum, and retrograde degeneration has been described by Morin (79) using Marchi methods, and by Daitz & Powell (30) and Powell & Cowan (88) using retrograde cell degeneration (Nissl) and fiber loss (Bodian) methods. The latter authors found no sign of cell degeneration in the hippocampal pyramids following section of the fornix. They explained this by supposing that the recurrent collateral fibers of the pyramidal cell axons maintain the activity of the pyramidal cells even though the more distal part of the axons were severed. Some of the Marchi degeneration, however, could be explained on the basis of afferent fibers in the fimbria and alveus. Ramón y Cajal (90) and many of the older authors described afferents from the septal area to the hippocampus, and Ramón y Cajal (90) specifically indicates that these afferents are not of

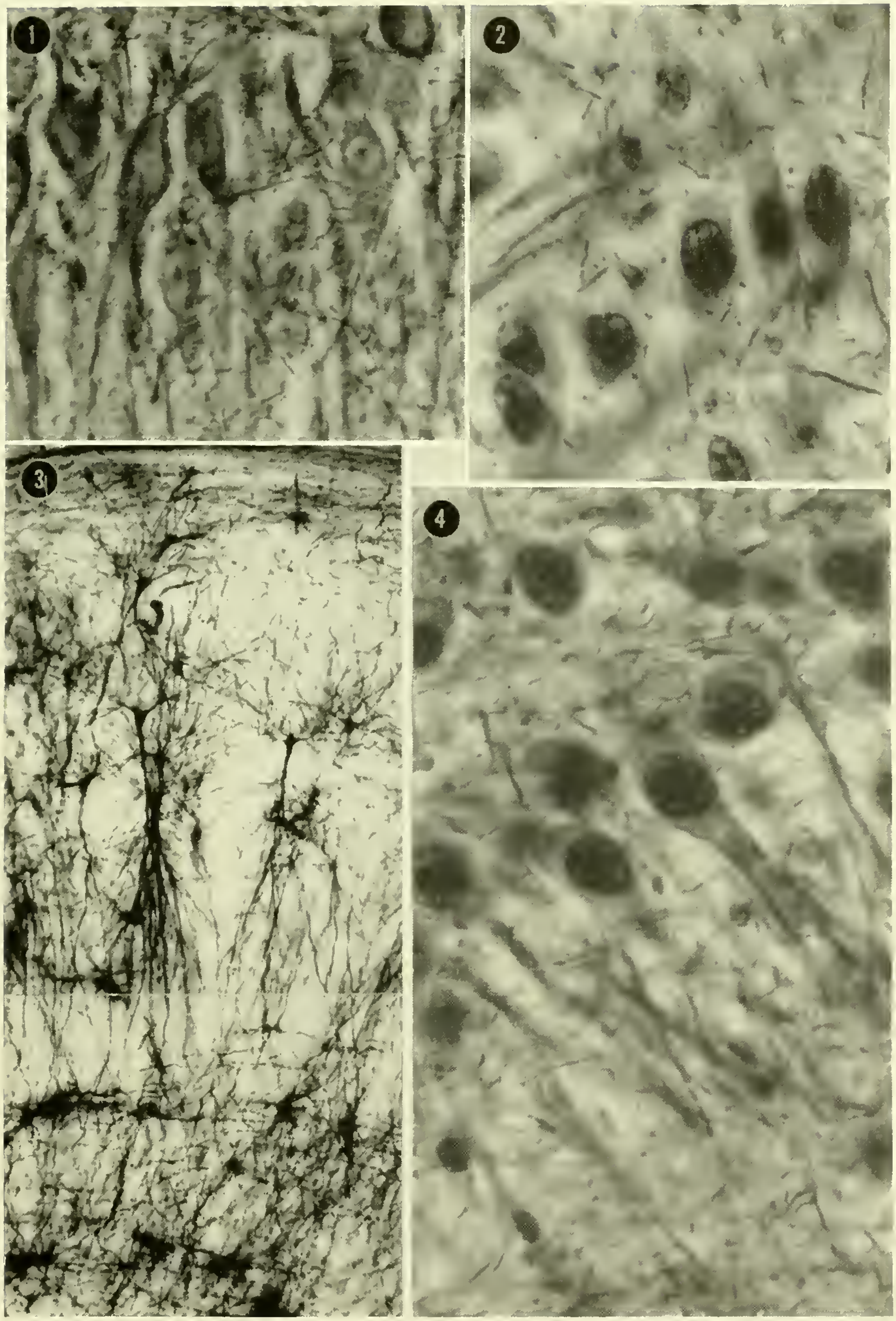

FIG. 4. Cell terminations in the hippocampus. *1*) Terminals about the hippocampal pyramids; Cajal VIa stain. *2*) Terminals in area h_3; Bodian stain. *3*) Terminals about the hippocampal pyramids; Sholl-Golgi stain. Note the temporoammonic tract below and alveus above. *4*) Terminals in area h_2; Bodian stain.

olfactory origin. Afferents probably reach the hippocampus from the reticular activating system of Moruzzi & Magoun (81) via the tegmentum and hypothalamus (45, 46). Morin (79) and Guillery (52) have described afferents from the mammillary penduncle into the medial forebrain bundle of mammillary nuclei.

More complex hippocampal pathways have also been proposed. In particular, the Papez (83) circuit requires mention. Papez conceived that a pathway from the anterior thalamus, to the cingulate gyrus, to the cingulum, to the hippocampus, to the fimbria, to the fornix, to the mammillary body and back to the anterior thalamus was concerned in emotion. That this pathway exists is true, and certainly stimulation of any point in this circuitous route evokes a response in any other point (45). However, for emotional processes it is probably not necessary that this circuit should be intact, although of course this does not exclude the possibility that some parts of the brain involved in the circuit are also involved in the perception, integration or expression of emotional changes. Connections with the amygdala have been demonstrated electrophysiologically (32, 41, 44, 45) and elaborate brain-stem connections of rhinencephalic structures have been proposed by Gloor (41).

Cell Terminations

Axons of the granule cells of the gyrus dentatus collect into a bundle of fibers which passes between the cells of fields h_5 and h_4 and comes to lie chiefly below the cells of field h_3. Here, they form a fairly distinct bundle from which branches spread further medially to fields h_2 and h_1. The terminals end around the basal parts of the apical dendrite and the soma of the hippocampal pyramidal cells, and occasional collaterals from these axons may be traced alongside the apical dendrite centripetally. Thus, afferent impulses reaching the granule cells are clearly relayed to the pyramidal cells of the hippocampus. Examples of these terminations appear in figure 4. The temporoammonic tract afferents seem to terminate axodendritically for the most part, both with respect to the granule cells of the gyrus dentatus and the pyramidal cells of the hippocampus. Since the actual terminals themselves are extremely hard to resolve with a microscope and are very small indeed, it is difficult in normal preparations to be certain whether the maximal termination is at this point or whether it is along the course of the apical dendrite toward the soma and around the soma, for branches may be seen from the temporoammonic tract which radiate centrifugally toward the somata of the pyramidal cells. These were described by Ramón y Cajal (90) and Lorente de Nó (73). In the hippocampus the temporoammonic tract fibers are most obvious in fields h_1 and h_2. In h_3 they are less prominent and are to some extent blended with the fibers from the axons of the granule cells of the gyrus dentatus. Lorente de Nó (72, 73) described afferents to both hippocampal pyramids and granule cells from the fimbria. These seem to consist of rather delicate fibers which divide as they approach the cells and terminate for the most part around the basal dendrites or the cell bodies. However, some fibers may be traced through the cell layer toward the apical dendrites where they travel parallel to these dendrites. Thus, the three types of afferents all have fairly general distribution with respect to the pyramidal cells; but the alvear afferents are chiefly distributed around the basal dendrites and soma, the fibers from the gyrus dentatus are distributed around the soma and the basal part of the apical dendrite, and the fibers from the temporoammonic tract are distributed around the apical dendrite with collaterals extending toward the soma and basal part of the apical dendrite.

FUNCTIONS OF THE HIPPOCAMPUS

The hippocampus has been studied from two somewhat different points of view. It has been of interest, first, because no clear role has been attributed to so large a part of the brain and, second, because, compared with the neocortex, its structure appears simple and therefore offers special experimental opportunities. It is peculiarly suitable for the study of field potentials and their significance.

Theories of Hippocampal Function

It was recognized by early anatomists that the hippocampus was large in animals in which the dominant special sense was smell. Since the hippocampus appeared relatively large in these macrosmatic animals, it was considered to form part of the rhinencephalon, the implication being that it was in some way concerned with olfactory processes. Neither Ramón y Cajal (90) nor Elliot Smith (103) considered that the hippocampus was exclusively olfactory in function although Elliot Smith (103) suggested that the dentate gyrus was, believing it to be absent in anosmatic animals. This misconception was clarified by Breathnach & Goldby (20) who showed that the porpoise

has a well-developed dentate gyrus despite the fact that the cetaceans are completely anosmatic and lack olfactory nerves. The hippocampus is often well developed in human monsters born without olfactory bulbs and is generally believed to reach its highest state of development in the microsmatic animal, man. The completely subordinate role of olfactory impulses in the function of the hippocampus was finally demonstrated by the experiments of Swann and of Allen. Swann (108, 109) showed that olfactory discrimination was not affected by ablation of the hippocampus. Allen (10, 11) demonstrated that olfactory conditioned reflexes still persisted after the hippocampus had been removed and also that they could be established after its ablation. Thus, the hippocampus is of minor significance even in highly coordinated olfactory reflex mechanisms (22, 65, 74).

Herrick's view that the hippocampus correlates the diencephalic and cortical structures is implicit not only in his own monumental studies (53, 54), but also in the earlier work of Ramón y Cajal (90, 91). Certainly no one can dispute this point of view, but the specific function is another matter and up to this time no truly satisfactory theory concerning the role of the hippocampus has been advanced. Ablation of the hippocampus, without serious damage to large areas of the brain, has not yet proved feasible. Electrolytic or surgical injuries, locally placed within the hippocampus without its total destruction, produce a variety of changes; but it is striking to note that these changes are remarkably similar to the changes seen following local stimulation in the conscious animal, and the question arises whether they are, in fact, the results of destruction or the results of irritation. Electrolytic or severe experimental infarction may give rise to a condition resembling psychomotor epilepsy (47, 48), and it is quite likely that some of the behavioral changes observed—abnormal fears, pupillary dilatation, anisocoria and hyperesthesia—may represent a part of the seizure process. This is particularly likely since these behavioral changes seem to be triggered by peripheral stimulation of various kinds. It is interesting to compare the seizures and behavioral changes observed following electrolytic lesions with the similar changes described after stimulation (14, 51, 61–63, 66–70, 76). Secondary damage to the hippocampus, induced by interruption of its blood supply (47, 48; Naquet, R., *et al.*, personal communication), seems to induce effects identical with those of electrolytic lesions placed exclusively in the hippocampus. The behavioral changes seen following lesions tend to occur particularly in the first 3 weeks postoperatively. This is usually followed by an interval which seems to be virtually symptom-free; but the effects may then recur after an interval of some months, suggesting the gradual formation of an irritative scar within the central nervous system. Apart from seizure discharges and their concomitant effects, stimulation of the hippocampus has yielded disappointing results. Kaada found that "it did not yield any significant effects on any of the somato-motor or autonomic activities recorded in this study (except for some facilitation of cortically-induced movements when the three central motor areas were activated)." Carlson *et al.* (25) believed that the autonomic effects seen following stimulation of the fornix and mammillary body could be attributed to the spread of current to adjacent hypothalamic areas; Penfield & Erickson (84) also obtained negative results. Kaada (61), however, saw pupillary dilatation in man, which can be confirmed for the cat, while Kaada & Jasper (63) observed changes in respiration, and MacLean & Delgado (76) saw changes in emotional behavior. Damage to the fornix and septum lucidum produces changes in rage threshold, according to Spiegel *et al.* (106) and Rothfield & Harmon (99). Green & Arduini (46) noted that lesions of the septum lucidum in rabbits, involving the precommissural fornix but not the postcommissural fornix, resulted in curious behavior in which the animals seemed to be hyperreactive and at times would apparently attack the observer in fear. They noted that this type of lesion blocks the theta rhythm; this will be discussed below. Brady & Nauta (18, 19) made somewhat similar observations on the rat but noted that after a period of about 40 days the response disappeared. Therefore, it is not clear whether the response is an irritative one or whether the recovery is due to some local process of adaptation. Section of the fornix, incidental to section of the corpus callosum, did not produce behavioral changes in man in the observations of Akelaitis *et al.* (6–8), while Wheatley (114) observed no changes following complete electrolytic destruction of the fornices (postcommissural fornix and partial damage to septum). Dott (31) noted no symptoms which could be attributed to section of the fornices and incision of the lower part of the septum lucidum in two patients. It should be pointed out, however, that in these patients there were also a number of signs of hypothalamic damage. Garcia-Bengochea *et al.* (36) also found no detectable changes in monkeys in a variety of performance tests. Possible roles of the hippocampus in conditioning and learning will be considered by Galambos & Morgan in Chapter LXI of

this work, and in emotional phenomena by Brady in Chapter LXIII.

Spontaneous Electrical Activity and Relation to 'Arousal' Mechanisms

Using the Hess implanted electrode technique, Jung & Kornmüller (60) observed a theta rhythm discharge of 4 to 7 per sec. waves in the rabbit hippocampus following afferent stimuli. In an exploration of subcortical electrical activity in the cat brain, Gerard *et al.* (38) noted somewhat similar rhythms in the cat brain. MacLean and co-workers (77) noticed olfactory-like 'responses' in the cat hippocampus following a variety of stimuli. These changes were seen in the pyriform cortex and in the hippocampus but the majority of the changes they reported were fast, perhaps to be explained from the fact that they observed animals under anesthesia. They mention, however, that they also saw a theta rhythm response similar to that of Jung & Kornmüller (60). Robinson & Lennox (93) saw evoked potentials following hippocampal stimulation. Liberson & Akert (67) observed a theta rhythm in the guinea-pig brain following what they term 'social intercourse.' Green & Arduini (46) studied the theta rhythm in the rabbit. They found that it could be elicited by a variety of stimuli, including visual, auditory, somatic and olfactory, as shown in figure 5. It was also seen in the cat, but with considerably more difficulty. In the monkey the evoked potential was not difficult to observe but the theta rhythm was virtually impossible to see, excepting under conditions likely to produce extreme emotional reactions. [This accords with the observations of Grey Walter (113) on man which are discussed in Chapter XI in this *Handbook*.] This

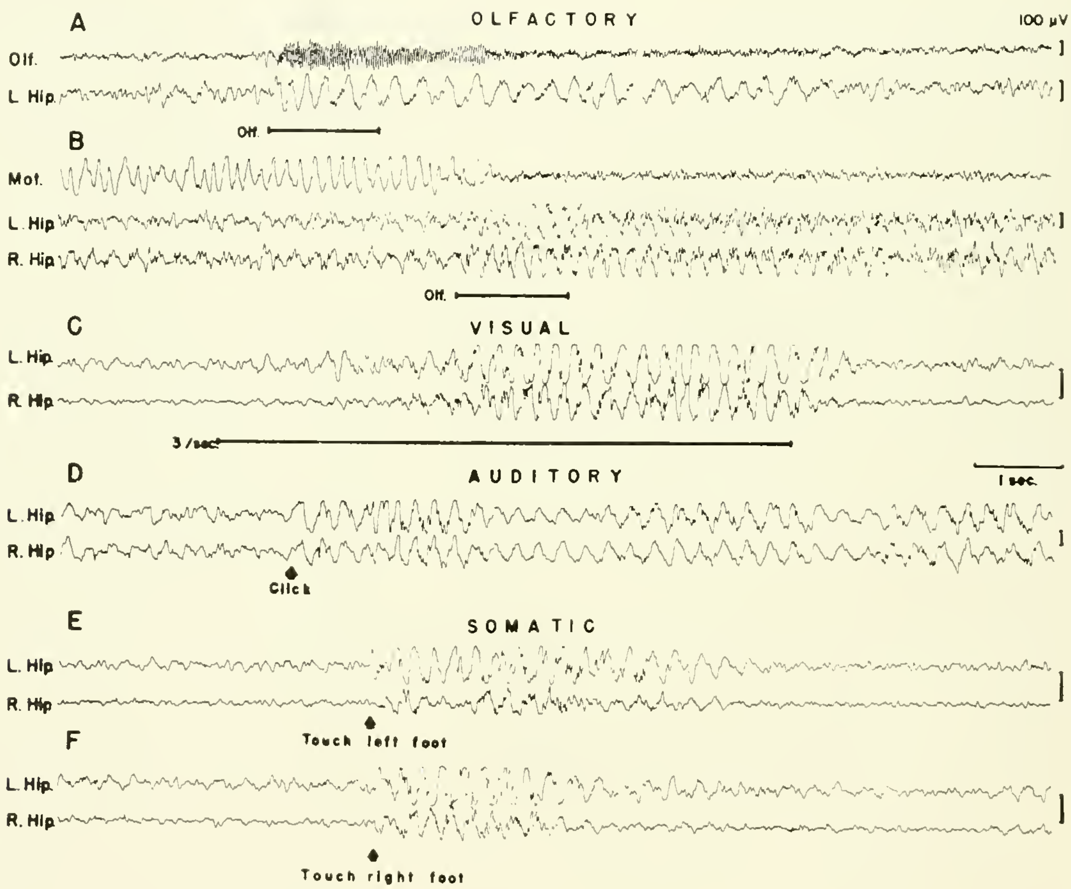

FIG. 5. Afferent responses in the hippocampus. Acute rabbit preparations under curare and local anesthesia, showing various afferent responses. *Olf.*, olfactory bulb; *Mot.*, motor cortex; *L.* and *R. Hip.*, left and right hippocampi. Note characteristic hippocampal responses to various modalities of stimulation. [From Green & Arduini (46).]

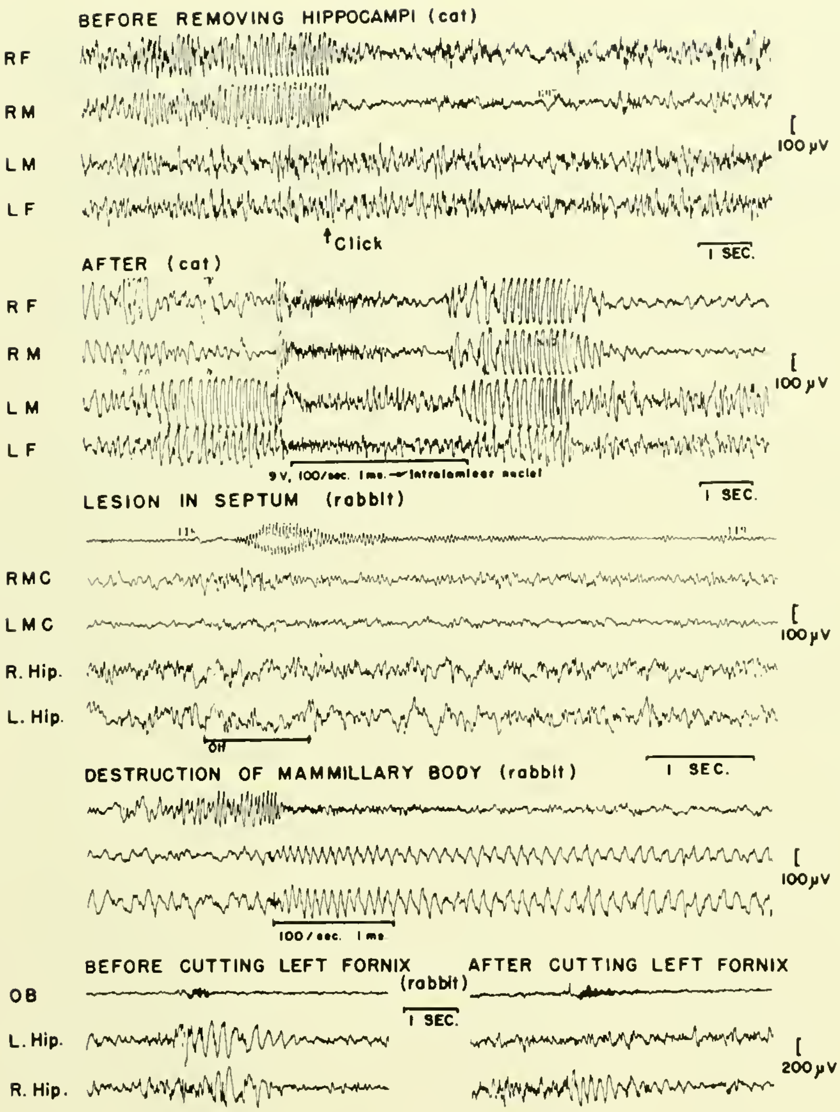

FIG. 6. Effect of lesions of the brain on cortical and hippocampal arousal. *RF*, right frontal cortex; *RM* or *RMC*, right motor cortex; *LM* or *LMC*, left motor cortex; *LF*, left frontal cortex; *R. Hip.*, right hippocampus; *L. Hip.*, left hippocampus; *OB*, olfactory bulb. In first two records it is shown that removal of the hippocampus does not entirely eliminate cortical 'arousal' response which follows stimulation of intralaminar thalamic nuclei. In *third record* it is seen that, after lesion in dorsal septal area (destroying much of septum above anterior commissure, precommissural fornix and part of rostral end of cingulate area), there was no hippocampal arousal to an olfactory stimulus. While this negative result is not striking, it should be emphasized that these rabbits were the only ones in which no hippocampal arousal could be evoked and it seems to correlate well with results of section of dorsal fornix (including precommissural fornix fibers). In *last record* effect of cutting left dorsal fornix in decorticate animal is seen. Note that response is abolished on ipsilateral side. [From Green & Arduini (46).]

rhythm could also be induced by stimulating the reticular activating system of Moruzzi & Magoun (81) from the midbrain tegmentum and from points extending through the lateral hypothalamus to the septum and back into the hippocampus. No theta rhythm, however, was ever induced by stimulation of the hippocampus directly. The theta rhythm could, however, be traced forward from the hippocampus into the fornix, mammillary body, mammillothalamic tract, toward the anterior thalamus, and it was felt that it could also probably be recorded from the habenulopeduncular tract, although it was conceivable that this was a volume conduction effect. They found that destruction of the mammillary body did not block the theta rhythm in the hippocampus and that stimulation of the mammillary body did not induce it. The theta rhythm was not blocked by lesions in the amygdala nor by removal of the entorhinal cortex. This latter point has been disputed by Carreras *et al.* (26) who were unable to find the theta rhythm after the entorhinal cortex was removed, but it has been confirmed on the other side by Adey *et al.* (2). Ricci & Sutin (personal communication) also stated thay they observed the theta rhythm after the entorhinal cortex had been removed but noted that before it reappeared a period of shock frequently ensued in their animals. Green & Arduini (46) concluded that afferents reached the hippocampus by way of the reticular activating system, hypothalamus and septum and that efferents left it by way of the

postcommissural fornix and mammillary body. An attempt was also made to remove the hippocampus to observe what effect this might have on the electrical activity of the neocortex. The results are shown in figure 6. After acute bilateral hippocampal ablation, the cortex was observed to spindle, as in the condition of relaxation or sleep, and it was found extremely difficult to induce arousal of the cortex by physiological stimuli. However, stimulation of the intralaminar nuclei still produced desynchronization of the neocortex but only for the duration of the stimulus itself. Since in the guinea pig stimulation of the anterior thalamus and intralaminar nuclei evokes a widespread recruiting response all over the cerebral cortex, and since stimulation of the septum produces the same effect (50), the possibility is suggested that the anterior thalamus and intralaminar nuclei may in someway be excited by the reticular activating system and hippocampus, or possibly septum, and thence influence the whole of the neocortex. Thus, stimulation of the intralaminar nuclei after ablation of the hippocampus might cause the desynchronization of the neocortex, but since the main afferent pathway to the anterior thalamus would be interrupted, physiological stimuli would fail to arouse the neocortex. Nevertheless, it must be remembered that this type of acute experiment was performed in a few instances only, that it is very traumatic and that the animal may have been comatose for other reasons, for example because of incidental damage to lower brain-stem structures or thalamus. It is interesting to note that Akimoto *et al.* (9) have recently reproduced Hess' (55) sleep reaction by stimulation of the anterior thalamus at low frequency but obtained arousal at higher frequencies.

Records from single cells in the hippocampus of the cat (15, 16) or rabbit (49) indicate that single cells are also responsive. Incidental observations of this kind were also made by Tasaki *et al.* (110) in the course of a study on the lateral geniculate body. In the case of visual stimuli, as shown in figure 7, Green & Machne (49) found that rhythmic unit bursts occurred at approximately the frequency of the theta rhythm although they were rarely, if ever, in exact phase. They had more difficulty in seeing any synchronization with other forms of afferent stimulation. Hippocampal units seemed to respond specifically to one mode of peripheral stimulation only, providing the electrode was in the hippocampal pyramids. About half a millimeter below the surface of the hippocampus, where the electrode would be expected to enter the dendritic layer, no spontaneous activity occurred. This persisted for a further 1.5 mm, after which units were again seen responding either to specific modalities or to a variety of modalities. At this time, presumably, the electrode tip was either in the granule cells of the gyrus dentatus or in area h_{4-5}. In this region, just within the layer of granule cells in the gyrus dentatus, there are a number of Golgi type II neurons which seem to link adjacent groups of dentate granule cells. This seems to suggest that there might be a one-for-one relationship between granule cells and pyramidal cells but that the Golgi type II neurons might respond to a variety of modalities.

The evoked potential following physiological afferent stimulation has not been studied greatly. It is readily seen in the monkey despite the difficulty of obtaining the theta rhythm. Green & Adey (45) noticed that it could be observed readily in the cat but seemed very sensitive to anoxia, and that it failed quickly with repetitive stimulation, responding best at intervals of about once every 30 sec. Adey *et al.* (2) have noticed both the evoked potential and theta rhythm in the Australian phalanger, *Trichosuras vulpecula*, where its characteristics seem to be not unlike those seen in the cat.

At present, then, we are not in a position to assign any specific functions to the hippocampus. Among suggestions that have been made are: *a*) that it is concerned in emotion (83), a view discussed by Brady in Chapter LXIII of this work; *b*) that it is concerned in visceral activity (65, 74); *c*) that it is concerned with memory mechanisms (78); *d*) that it is part of a general forebrain suppressor system (61); *e*) that its activity might, in some way, be the converse of that of the neocortex on the reticular activating system (46). At the present time none of these suggestions can be taken altogether seriously. However, it is possible that the rhinencephalon, playing upon the rostral part of the reticular activating system, in some way modulates the activity of the cerebral cortex, perhaps enhancing or suppressing it, or being concerned with preservation of activity within the cerebral cortex. All speculations about memory, emotion and visceral activity face one serious stumbling block: the susceptibility of the hippocampal formation to seizure discharge, for if seizures may result either from stimulation of the hippocampus or from lesions in the hippocampus, and if these seizures spread to other areas of the brain, then great restrictions must be placed upon the interpretation of data depending upon stimulation or lesion-making, for the seizure effects may arise not from the hippo-

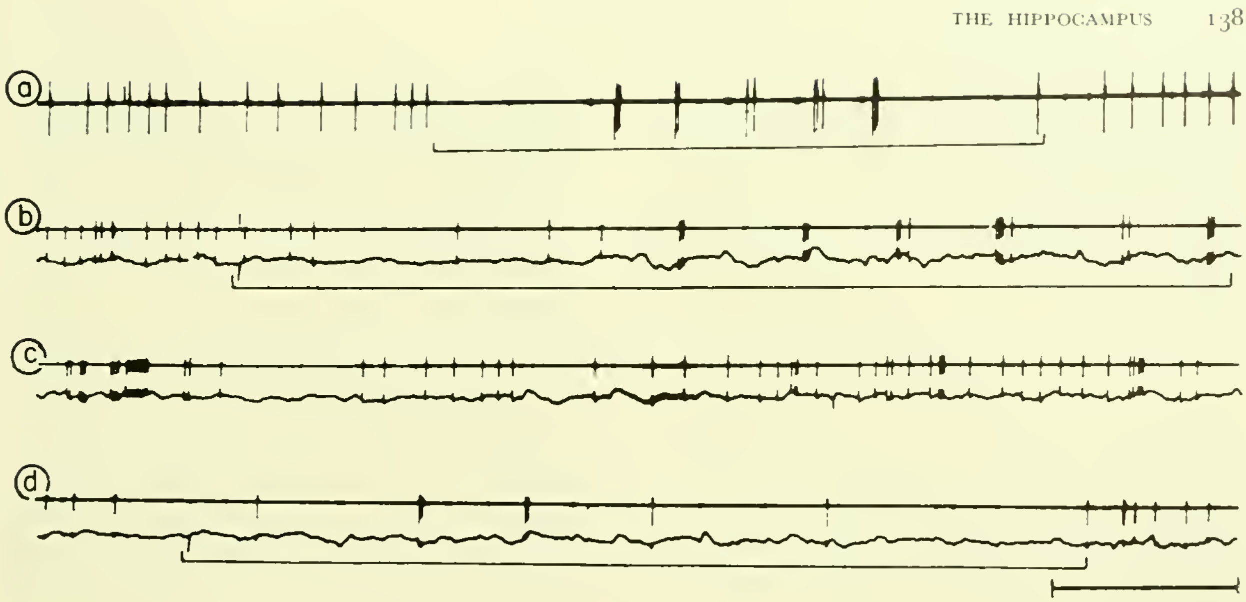

FIG. 7. Activity recorded from a single unit at the level of the lower hippocampal pyramids gain higher for *a* than for *b*, *c* or *d*. Records *a* and *b* show the effect of a flashing light. (A smal second unit's activity is detectable in *a* which also shows regular bursts on stimulation, but is no precisely in phase with the large one.) Record *c* is of spontaneous activity; *d*, of continuous visua excitation. The unit was not affected by other modalities of sensory stimulation. [From Green & Machne (49).]

campus itself but from some other region in which seizure activity is induced.

Field Potentials and Unit Activity

Renshaw *et al.* (92) in an early study of subcortical unit activity investigated the hippocampus and drew attention to the advantages of its single lamina of cells. While the neocortex has six recognized laminae in which axons, dendrites and cell bodies are almost inextricably intermingled, the pyramidal cell layer of the hippocampus is arranged with the somata tightly packed together, with the apical dendrites passing centripetally and the axons and basal dendrites passing at first centrifugally. The axons then turn in the alveus at right angles forming a thin surface layer. The hippocampus may be approached by removing the cortex and corpus callosum above the lateral ventricles in animals which possess a dorsal hippocampus, such as the cat. The blood supply enters the hippocampus from the septal arteries, a series of branches which emerge from an arterial arcade formed by the anterior and posterior choroidal arteries. This group of septal vessels penetrates between the gyrus dentatus and the hippocampus and supplies Ammon's horn from this cleft which, however, is incompletely filled with pia and is crossed by part of the temporo-ammonic tract system of fibers. The result is that when the hippocampus is exposed from above, it is approached via the ependyma rather than the pia. Its blood supply entering from below is not endangered. Under these circumstances, Green & Adey (45) were able to isolate the hippocampus by sectioning the fornix and the psalterium, and by removing the entorhinal cortex and amygdala. A single hippocampus isolated in this way is silent during acute experiments lasting several hours. A single shock applied to the hippocampus may be followed by an evoked potential in almost any other part of the structure. A single shock to the fornix under these circumstances also activates the hippocampus. If this response is recorded with active electrodes on the surface of the hippocampus, it is found not to be altered by making a circumscribed cut around the point from which the record is taken (45, 112), providing this cut extends half a millimeter or so, and no more, beneath the surface. A deep cut, parallel to the fimbria, abolishes or greatly modifies the response. It was concluded that the response recorded with a latency of 4 to 5 msec. was postsynaptic, for it was greatly depressed by anoxemia and by pentobarbital, and it was potentiated by strychnine or by repetitive stimulation and showed, in addition, tetanic and posttetanic potentiation. It was also concluded that the afferents

evoking the response did not reach the hippocampal pyramids through the alveus. The possibility of direct axon collaterals, therefore, seems rather remote. The usual point of recording corresponded roughly to field h_2. It is conceivable that axon collaterals, activated antidromically in, say, area h_3 secondarily activate neurons in area h_2. Since the latency of the response was about 4 msec., it was considered that at least two synapses might be involved. Since Lorente de Nó (72, 73) had described afferent pathways reaching the dentate gyrus from the fimbria, it seemed not unreasonable that the primary relay might be in the dentate gyrus, that the known pathway from the granule cells to the pyramidal cells might be involved, and that the secondary relay would then be in the pyramidal cells. von Euler *et al.* (112) presented evidence that the main region of depolarization, following stimulation of the fornix, was around the soma and basal part of the apical dendrite, but they believe that repetitive stimulation produces successively greater dendritic depolarization. Gloor (42) noted unit-like activity in the dendritic layer following repetitive stimulation. Buser & Rougeul (24) recorded intracellularly in the hippocampal pyramids and noted that the spike from the soma was followed by a prolonged hyperpolarization which they attributed to the dendrites.

Seizure Discharges

Jung (59) demonstrated that, following electroshock, the hippocampus showed the lowest threshold of any region in the cerebral hemisphere. Kaada (61), by direct stimulation, found that the hippocampus was second only in sensitivity to the pyriform-amygdaloid region. Green & Morin (50, 80), Green & Shimamoto (51), Segundo *et al.* (100) and Creutzfeldt (29) determined that in curarized animals the hippocampus had an exceedingly low threshold and that it could be stimulated to paroxysmal electrical discharge simply by the insertion of an electrode, by lightly stroking the fimbria with a thread of cotton soaked in saline or by pricking it lightly with a fine needle. Andy & Akert (14) also found a very low threshold but suggested that tubocurarine had influenced the level of excitability. Liberson & Cadilhac (68–70) similarly found an exceedingly low threshold, as low as any other part of the brain. The concensus supports this observation. Personal experience indicates that in the unanesthetized animal the threshold is virtually as low as in the curarized animal. Seizure discharges propagate from the hippocampus in all directions, but they are not dependent upon external connections. Thus, seizure discharges can easily be induced in the isolated hippocampus (45), as well as after severing the hippocampal connections one by one (51). Morin & Green (80) and Green & Shimamoto (51) found that the seizure discharges were propagated into the temporal lobe even though the fornix was severed. At first sight, it would seem reasonable that the generalization of the hippocampal discharge might be through the fornix, mammillary body and anterior thalamus, and thence, diffusely, to the rest of the hemisphere. However, generalized discharges in the hemisphere may be induced even after the fornix has been completely removed by suction, together with the thalamus, hypothalamus and reticular activating system back to the midbrain tegmentum (51). A clue to a possible way in which this may occur is suggested by the studies of Green & Adey (45) and Adey *et al.* (2) who found that stimulation of the hippocampus evoked responses in the entorhinal area in apparent opposition to the main known anatomical course of axons in this region. However, von Euler *et al.* (112) also obtained evidence that seizure discharges might propagate ephaptically from the hippocampus, via dendritic processes (perhaps to the entorhinal cortex), and such propagation is not unlikely in view of the observations of Bremer (21) on the synchronization of strychnine seizures in the cord, those of Gerard & Libet (37) on the caffeine wave in the frog brain, and those of Rosenblueth & Cannon (98) and Rosenblueth *et al.* (97) on seizure discharges in the cat cortex. The conclusion may, indeed, be drawn that seizure discharges propagate both by axonal pathways, for example in the so-called reflex epilepsies of Amantea (13), as was demonstrated long ago by Bubnoff & Heidenhain (23), and by routes which are not strictly anatomical pathways but simply regions of contiguity.

Liberson & Cadilhac (69) have carried out studies on hippocampal seizures in the guinea pig. In particular, they have undertaken to measure seizure thresholds in terms of number and duration, as well as amplitude of applied pulses, and have observed direct current shifts in hippocampal seizures. von Euler *et al.* (112) also observed a direct current shift during hippocampal after-discharges and found that the dendritic layer tended to show a negative shift whereas the axonal layer on the surface of the hippocampus shifted in the opposite direction. Thus, the seizure seems to induce a polarization of the cell somewhat along the lines visualized by Gesell (40) or by Libet & Gerard (71).

In cats electrolytic lesions in the hippocampus induce seizures which show most of the characteristics of psychomotor epilepsy (47). Seizures may also occur as the result of secondary injury to the hippocampus when the region of primary destruction is elsewhere, particularly in the amygdala (47; Naquet, R., *et al.*, personal communication). Lesions involving the medial part of the amygdala in the cat frequently interrupt the anterior choroidal artery. When this happens, there is a destruction of many of the cells within the hippocampus, both ventral and dorsal. Animals with this type of lesion show motor fits, usually of a clonic type, with a march from the face through the neck, forelimbs, trunk, to the hind limbs, accompanied by salivation and often preceded by prodromal 'arrest reactions' or by more complex signs, for example pouncing as if to catch a small animal, striking or patting at the air, or signs suggestive of fear. Very often these seizures may be triggered by peripheral stimulation, by touching the animal, by repetitive click stimulation or by stroboscopic stimulation. The same forms of stimuli also at times induced what appeared to be sensory fits. The animals may show apparent fear, retreating from the investigator, crouching at the back of the cage, snarling and hissing, and showing dilated pupils and piloerection. Sometimes this does not appear instantaneously but only after a more or less prolonged period of afferent stimulation. Sometimes when the animal is stroked, regions of hyperesthesia seem to appear and the animal will strike out at the investigator when certain parts of the body are reached, especially in the region of the pelvis and axilla. The onset of such a 'seizure' is most commonly initiated by an arrest reaction in which the animal suddenly ceases whatever it is doing, remains motionless for a few seconds and possibly looks around in a worried fashion. At times such behavior is not accompanied by any further signs, although after a period of peripheral stimulation, as previously described, the animal may show what seem to be unreasoning fears, for example fear of kittens or of other small animals. Studies on conditioning by MacLean (75) and by Lissak (personal communication) seem to indicate that hippocampal stimulation will cause the arrest of a conditioned response.

General Conclusions on Functional Role of the Hippocampus

Because of the susceptibility of the hippocampus to seizure discharges, and because these seizure discharges are accompanied by a condition resembling psychomotor epilepsy notably associated with prodromal signs and hallucinations, it is evident that at the present time great caution must be applied in interpreting its functional role. This caution is especially emphasized by the absence of clear-cut effects resulting from destruction of the main efferent pathways in the fornix. The rhinencephalon occupies a phylogenetic position midway between those of the reticular activating system, the midbrain tegmentum and thalamus, and that of the neocortex. Within the rhinencephalon the hippocampus and piriform cortex may be considered to represent the ancient cerebral hemisphere, or ancient cortex, of primitive vertebrates. It is reasonable to suppose that, of all rhinencephalic structures, the hippocampus represents perhaps the highest level of integration. It is clearly established that it is in important relationship with the reticular activating system and it seems reasonable to suppose that it modifies the latter's activity, but at the present our knowledge has done little more than confirm the predictions of Herrick in 1933 (53). However, evidence is accumulating to suggest the participation of Ammon's horn in 'emotional' responses.

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Electrical stimulation of the hippocampus in man

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A CONSIDERABLE VOLUME OF DATA has accumulated in the literature on the physiology of the hippocampal region since publication of the contradictory interpretations of Ferrier (5), Spencer (23) and Ossipoff (14) based on experimental work on animals. Recently Kaada (9), Macchi (13), Gastaut (6), Cadilhac (1), Green & Adey (8) and Green in the preceding chapter of this work have added to our knowledge of the function of the hippocampus in animals and reviewed the previous papers on the subject.

Electrophysiological observations in man however are scanty, and small groups of patients have been studied without uniform technique and often without anatomical control. The difficulty of approaching the hippocampal region in man is probably the main reason for the small number of published reports in spite of the growing interest of clinicians and neurosurgeons in the possible role of this area of the brain in health and disease.

The nomenclature of the cerebral structures included in the so-called rhinencephalon of man is somewhat confused in the literature [for discussion see (1, 13)]. In the present review we shall make a distinction between the hippocampus (Ammon's horn, cornu ammonis or hippocampal formation, including the gyrus dentatus) and the hippocampal convolution (gyrus hippocampi, fifth temporal convolution or gyrus uncinatus).[1] The hippocampus forms the floor of the temporal horn of the lateral ventricle and the hippocampal fissure separates the hippocampus proper (including the subicular region) from the hippocampal convolution. Ontogenetically both the dorsal and the rostral hippocampus in man undergo very early regressive changes and these structures have probably only vestigial importance after fetal life, in contrast to certain animals where the olfactovegetative association areas remain extensive (12, 13). The uncus is the rostral portion of the hippocampal convolution and is therefore separate from the hippocampus proper. The vague term of hippocampal region will be used in this paper to include the hippocampus, the hippocampal gyrus and the uncus.

The few observations upon the effects of electrical stimulation of the hippocampal region in man in the literature fall into three main groups according to the approach used.

a) Stimulation of the hippocampal convolution, uncus, tip of the temporal lobe and the region of the amygdaloid complex has been undertaken in the intact brain by applying the stimulating electrodes to the cortex of the inferior surface of the temporal lobe after it had been lifted slightly from the floor of the middle fossa. This approach has been used by Chapman *et al.* (3), Liberson *et al.* (11), Kaada (9), Sloan *et al.* (22), Kaada & Jasper (10), Glusman *et al.* (7), Pool (21), Chapman *et al.* (4) and Penfield & Jasper (20).

b) The proximal end of the hippocampus has been stimulated during the operations of hemispherectomy or temporal lobectomy after most of the temporal cortex had been removed. The stimulating electrodes were placed either on the cut surface of the hippocampus or on its superior surface. Workers using this technique include Penfield &

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[1] 'Hippocampal convolution' as used in this chapter is equivalent to 'entorhinal area' as used by Green in the preceding chapter—[Ed.].

Erickson (19), Passouant *et al.* (17), Passouant *et al.* (18), Penfield & Jasper (20), Pool (21) and Cadilhac (1).

c) Stimulation of the upper surface of the hippocampus has been accomplished with minimal interference to surrounding structures by approaching it through the ventricle without severing the anterior or inferior part of the temporal lobe, as has been done by Pampiglione & Falconer (15, 16).

One must remember that in all these observations the experimental subjects were patients with some disorder of cerebral origin, often involving the stimulated areas. Hence a full evaluation of the results is difficult. In addition the methods of stimulating differed widely from one observer to the other; square wave pulses, sine waves, saw-tooth waves have been used with a variety of pulse frequencies and duration. Furthermore the patients studied were either under general or under local anesthesia. It is not surprising therefore that no uniformity of results has been found. However, some patients with similar disorders were stimulated under comparable conditions, and in these certain valid comparisons may be made.

In patients in whom electrical stimulation was applied to the inferior surface of the temporal lobe, as in *a*) above, arrest of respiration appeared to be the most commonly-elicited phenomenon. Kaada (9), quoting his observations with Penfield and Jasper in eight patients stimulated under local analgesia with 4 v. saw-tooth waves at 60 per sec., says that arrest of breathing could be obtained from points on the anterior portion of the hippocampal gyrus and adjacent portion of the temporal lobe. Arrest of breathing however also followed stimulation of the insula. The respiratory arrest was invariably in expiration and appeared promptly upon application of the stimulus and lasted during the entire period of stimulation (3 to 30 sec.), occasionally interrupted by a deep breath. Mechanical stimulation (suction) in the same area produced respiratory arrest in one patient for 56 sec. This author mentions that his patients were partly able to overcome the respiratory arrest when asked to count, but there was also some tendency to close the eyes and to feel tired and sleepy. This comment appears of particular importance as it suggests that the apparent loss of contact recorded after hippocampal stimulation by Cadilhac (1) and Pampiglione & Falconer (16) was probably not related only to respiratory arrest. An interference with breathing was found by Glusman *et al.* (7) to follow stimulation of the uncus in six psychotic patients (4 to 12 v. square pulses lasting 2.5 to 5.0 msec. at a rate of 30 to 100 per sec. being used). Arrest of respiration however was also recorded by other workers stimulating not only the hippocampal region (3, 11, 17, 21) but also other regions of the temporal lobe, the frontal lobe, the thalamus, etc. [for discussion see (1)]. Thus, it seems possible that the respiratory arrest appearing after stimulation in man may not be a specific feature of any of the stimulated areas. Moreover Pampiglione & Falconer (unpublished observations) noticed that respiratory arrest produced by stimulating the hippocampus appeared only in their patients under general anesthesia and not in their conscious patients. Similar comments might be made concerning the observation of mydriasis reported by some authors as discussed by Cadilhac (1).

Stimulation of the hippocampus after temporal lobectomy, as in *b*) above, produced no observable changes according to Penfield & Erickson (19), but Pool (21) and Passouant *et al.* (17) noted in some cases mydriasis and in others respiratory arrest without fall in arterial pressure. One of the 15 patients operated upon under local anesthesia by Passouant *et al.* (17) clearly appeared to stop his conversation with the anesthetist at the time of the hippocampal discharge, which followed stimulation, and was unresponsive when called by name or when sensory stimuli were applied. It is not specified whether the operation had been performed over the dominant or nondominant cerebral hemisphere. In most instances the clinical phenomena produced by electrical stimulation of the hippocampus after removal of the surrounding structures of the temporal lobe or even after hemispherectomy were few (18). In fact Passouant *et al.* (17) remark that the importance and complexity of electrical manifestations after stimulation of Ammon's horn contrast with the poverty of concomitant peripheral phenomena.

In order to assess whether the poverty and inconsistency of the clinical manifestations elicited might be due mainly to the extensive surgical interference used by other workers, Pampiglione & Falconer (15) devised a new approach to the hippocampus, as in *c*) above, somewhat reminiscent of that used by Ferrier in a monkey (5). The brain was exposed by a lateral craniotomy and, after preliminary corticographic exploration, an oblique incision about 2 cm long was made in the midtemporal convolution, 5 to 6 cm behind the temporal pole, opening into the temporal horn of the lateral ventricle. Under direct vision through this incision a silver-silver chloride

ball electrode (1 mm in diameter) was slipped over the anterior portion of the hippocampus, the walls of the temporal horn keeping the electrode and its insulated flexible lead in place. A second electrode of the same type was placed over the superior surface of the hippocampus about 2 or 3 cm behind the first. Other electrodes were placed over the surface of the lateral aspect of the exposed temporal cortex in front of and behind the cut, and over the exposed frontal and parietal lobe. Still other electrodes were slipped under the orbital frontal cortex, the temporal pole, the uncus, the anterior and the posterior part of the hippocampal, the fusiform convolutions, or both of the last two structures. Scalp electrodes had been secured over the contralateral hemisphere.

This arrangement was devised in order: *a)* to ensure that the electrodes in the depth were actually in contact with the superior surface of the hippocampus with but little disturbance of the brain in its immediate proximity; *b)* to record the spontaneous activity of the hippocampus simultaneously with that of the cortex of the hippocampal gyrus, temporal pole, uncus and other regions of the brain when their connections were still intact; and *c)* to collect data on the subjective and objective phenomena evoked by electrical stimulation of the hippocampus in conscious patients.

The stimuli used were 50 per sec. square pulses of 3 msec. duration at 3 to 4 v. (occasionally 6 to 10 v.) applied through the electrodes placed on the hippocampus for periods from 2 to 10 sec. In contrast to other workers Pampiglione & Falconer did not attempt to establish 'threshold values' for either electrical discharges or clinical phenomena as their aim was to evoke clinical responses immediately without preliminary alteration of the 'excitability' of the area. All 17 patients were suffering from seizures deemed to be of temporal lobe origin and were going to be submitted to temporal lobectomy. Each one had shown over a period of several months to several years definite EEG abnormalities mainly in the temporal regions. In each patient stimulation of the hippocampus was performed at least twice, without displacing the electrodes, the intervals between stimulations varying from 5 to 20 min., with a total of 53 stimulations. The temporal lobe later removed in one piece, including the uncus and the anterior 3 to 4 cm of the hippocampus, was studied histologically by Cavenagh & Meyer (2).

The clinical and electrographic features varied a great deal from one patient to another and even in the same patient for similar parameters of stimulation. On no occasion did a major seizure occur even when 10 v. were applied. No constant relationship was found between the duration and pattern of the electrical changes and the type and duration of subjective and objective clinical phenomena. Clinical phenomena closely similar to the patient's spontaneous aura or attack were evoked on some occasions, including 'peculiar sensations,' complex hallucinations, apparent confusion and speech disturbances. On other occasions the evoked clinical phenomena were of a kind apparently different from the patient's spontaneous manifestations. Hallucinations of taste and smell occurred only once. But often there was a loss of contact with the patient who, for a few seconds up to over 1 min., was unresponsive to sensory and verbal stimuli and subsequently had amnesia for this period. Sometimes no clinical changes were noticed either objectively or subjectively in spite of prolonged electrical storms being induced, and at other times the clinical phenomena outlasted the electrical changes recorded.

The distribution of the electrical discharges was less variable and on no occasion were gross changes seen after hippocampal stimulation in the orbital and lateral frontoparietal cortex or in the contralateral temporal scalp record. Often the discharges were limited to the areas of one or the other, or of both, electrodes placed over the hippocampus. The temporal pole, the uncus, the hippocampal and fusiform convolutions were also commonly involved in the discharges either with or without participation of the anterior half of the lateral aspect of the temporal cortex. On the other hand temporal regions on the lateral aspect behind the level of the cortical incision were less often involved.

It is interesting to note that, although the clinical phenomena elicited by Pampiglione & Falconer (15, 16) with this technique were numerous in comparison with the reports of other authors, there was a considerable variability not only from one patient to another but even in the same patient when stimulation was repeated without displacing the electrodes and without alteration in the parameters of the stimulus. In a second report on their experiments, Pampiglione & Falconer (16) emphasized that, in contrast with the observations reported in animals, electrical stimulation of the hippocampus in man was never accompanied or followed by genital sensations, sexual phenomena, tactile sensations, gross behavioral changes, rages, or prolonged tonic or clonic movements.

In contrast with the extreme variability of the

clinical phenomena observed by the various authors, there is very little disagreement about the type of electrical discharges that may follow stimulation of the hippocampus in man. The excellent descriptions and illustrations of Cadilhac (1) show that there is a tendency for prolonged rhythmic discharges in the hippocampus. There seems to be a rather low threshold in man as well as in other animals for the afterdischarges that follow either electrical or mechanical stimulation of the hippocampus, but this might vary somewhat according to the extent of the histological abnormalities that might be present in one patient and not in another. In fact increased threshold and smaller discharges have been reported by Passouant *et al.* (18) in two of their four hemispherectomized patients; in these two extensive hippocampal gliosis was found Similar impressions have been described by Pampiglione & Falconer (16), since in their group of 17 patients in whom histological examination of the excised temporal lobe and hippocampus was made, very poor discharges were evoked from the hippocampus in four patients with severe sclerosis of this structure.

We may conclude this short review on some effects of electrical stimulation of the hippocampus in man by emphasizing that the functional significance of this structure is still unknown. Various hypotheses have been advanced since Ferrier (5) cautiously suggested that a center for touch might be located there. The detailed observations in man are sparse and somewhat inconsistent, and even the contribution of the conscious patient who tries to transmit to the observer the wealth of the subjective manifestations has so far failed to support the view that the hippocampus might be a structure with a single, definite and invariable function.

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CHAPTER LVIII

Amygdala

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CHAPTER CONTENTS

ANATOMICAL INTRODUCTION

THE AMYGDALA (synonyms for which are the amygdaloid nucleus and the amygdaloid complex) is a subcortical formation of the rhinencephalon or limbic system. It is included within this system on the grounds of its phylogenetic history and its fiber connections. In mammals it represents a mass of gray matter lying in the depth of the temporal lobe ventral to the lentiform nucleus with which it is partly continuous. In the human brain (255) it is part of the uncus of the hippocampal gyrus and lies anterior to the rostral end of the pes hippocampi from which it is separated by the thin ventricular cleft forming the tip of the temporal horn of the lateral ventricle. Although essentially a subcortical structure, the amygdala emerges to the cortical surface with its medial part, thus participating in the formation of the cortex of the uncus in man or of the anterior piriform lobe in lower mammalian forms.

The amygdala is subdivided into several subnuclei which can be identified in all mammalian brains[1] (fig. 1). These are usually grouped into two nuclear complexes (122): *a)* the basolateral complex with the lateral, the accessory basal and the basal nuclei (the latter being further subdivided into a large-celled lateral and a small-celled medial portion) and *b)* the corticomedial complex with the central, medial and cortical nuclei, the nucleus of the lateral olfactory tract and the corticoamygdaloid transition area. Both basolateral and corticomedial complexes merge anteriorly into the anterior amygdaloid area (62, 109) and more posteriorly are separated by the small-celled intercalated masses (109). The designation of

[1] They have been described in detail for many mammalian forms: marsupials (26, 131, 162, 191), Insectivora (47, 235, 246), Chiroptera (122, 131, 235), rodents (32, 109, 131, 242, 243, 246, 256), Edentata (233, 235), Carnivora (62, 130, 184, 247), Ungulata (69), Proboscoidea (235), Cetacea (1, 30, 156), primates (49, 131, 132, 157, 184, 247) and man (31, 46, 118, 132, 164, 177, 235).

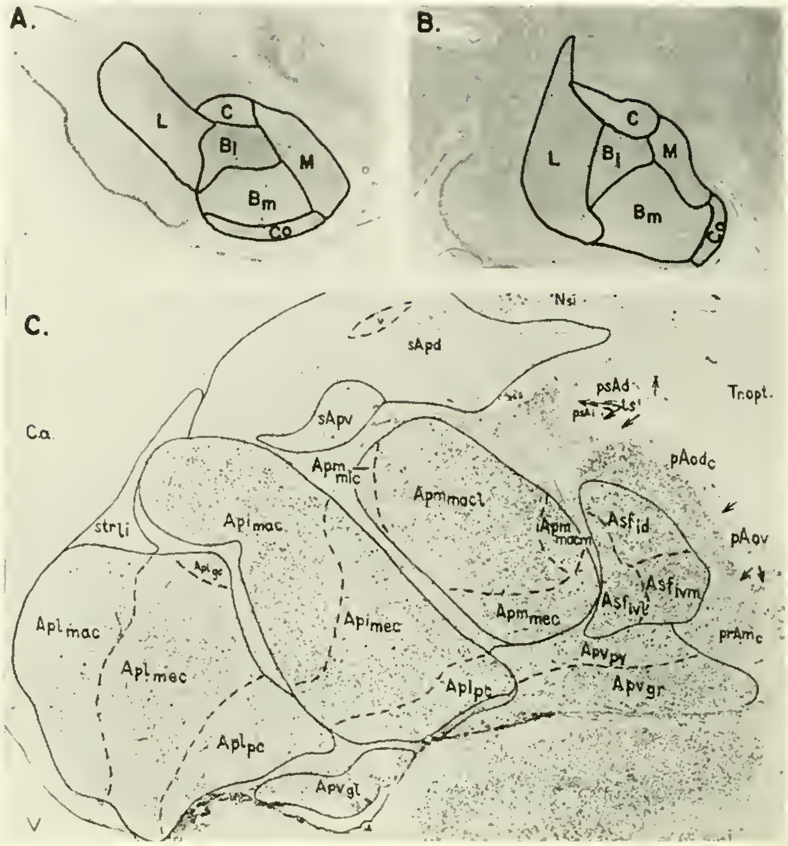

FIG. 1. Nuclear subdivisions of the amygdala in different mammalian species (Nissl stain). *A*: opposum; *B*: cat; *C*: man. (*A*, *B* and *C* are all frontal sections oriented in the same way with medial to the right and lateral to the left. *V*. in *C* indicates the tip of the temporal horn of the lateral ventricle.) *A* and *B*: *L*, lateral nucleus; B_l, basal nucleus, lateral (large-celled) portion; B_m, basal nucleus, medial (small-celled) portion; *C*, central nucleus; *M*, medial nucleus; and *Co*, cortical nucleus. *C*: *Apl* with its subdivisions corresponds to the lateral nucleus; Api_{mac} and Api_{mec} to the lateral portion of the basal nucleus; *Apv* with its subdivisions and probably also Api_{pc} to the medial portion of the basal nucleus; *Apm* with its subdivisions to the accessory basal nucleus which cannot be clearly identified in the opossum and the cat; *Asf* and *pA* with their subdivisions to the cortical nucleus; $prAm_c$ to the corticoamygdaloid transition area which can be clearly identified only in primates; *sApv* and perhaps *sApd* to the central nucleus. The medial nucleus is represented by the area lateral to *psAi* wedged in between *sApd*, Apm_{macl} and Asf_{id}. [*A* is a photograph of an original slide in Dr. E. C. Crosby's collection. *C* is taken from Brockhaus (31).]

the nuclei as 'lateral,' 'medial,' etc., indicates their position in low mammalian forms only (fig. 1*A*). Due to the expansion of the neopallium, the amygdala is rotated in higher forms until finally in man the lateral nucleus occupies a ventral and the medial nucleus a dorsal position (fig. 1*A*,*B*,*C*) (46, 132, 137). Parallel to this there is a gradual reduction of the corticomedial complex and a continuing development and differentiation of the basolateral complex which attains its highest complexity in man (31, 46, 118).

Ontogenetic and phylogenetic studies show that the corticomedial and basolateral complexes have a pallial matrix, whereas the corticomedial complex is subpallial in origin (119, 132, 164). The corticomedial complex is phylogenetically older and its primordium can be traced back to the cyclostomes (48). A well-circumscribed amygdaloid 'nucleus' appears first in tailless amphibians, at which stage it originates in parallel to the emergence of the vomeronasal organ of Jacobson, from which, in these forms, it receives its main afferent inflow (113). At this low evolutionary level the general plan of efferent amygdaloid connections of higher forms is already laid down. One system of fibers, including the dorsal olfactory projection tract of Ramón y Cajal (208), crosses the lateral forebrain bundle dorsally and reaches the septum, the preoptic region and the hypothalamus; it corresponds to the stria terminalis of higher forms which swings dorsally around the enormously enlarged lateral forebrain bundle, now called the internal capsule. Another system of fibers runs from the amygdala to septal and preoptic regions crossing the lateral forebrain bundle ventrally. It corresponds to the diagonal band of Broca and other less well-defined ventral amygdalohypothalamic tracts of higher forms running below the internal capsule. To this primitive amygdala, which they inherited from their amphibian ancestors, the reptilians add a new element of hypopallial origin. It forms the posterior part of the dorsal ventricular ridge and probably corresponds to the basolateral complex of mammals (37, 45, 48, 119, 132, 137).

ANATOMICAL AND PHYSIOLOGICAL STUDIES OF AMYGDALOID CONNECTIONS

Afferent Connections

OLFACTORY CONNECTIONS AND OLFACTORY FUNCTIONS OF AMYGDALA. Among the afferent connections of the

amygdala only the olfactory fibers are anatomically well defined. These fibers originate in the olfactory bulb and reach the amygdala mainly via the lateral olfactory tract. They terminate in the corticomedial complex (2, 8, 42, 109, 122, 130, 132, 157, 162, 180, 191). Some fibers cross the mid-line in the anterior commissure and reach the contralateral amygdala (2, 42).

In the amygdala evoked potentials to electrical stimulation of the olfactory bulb may be recorded from the cortical nucleus which forms part of a larger primary olfactory projection area covering the whole periamygdaloid cortex (39, 65, 133, 214).

When the olfactory bulb is stimulated with long pulses (27) or with tripled electrical stimuli (120) evoked potentials can be elicited in the whole extent of the amygdaloid complex. However, under these conditions the amygdala is merely a part of a much larger cortical and subcortical field activated by olfactory bulb stimulation which includes large parts of the striatum, thalamus, hippocampus, brain stem and cerebellum. In all these areas there is extensive overlap of olfactory evoked potentials with responses evoked by other sensory modalities (52, 120), and therefore these areas have to be considered as an unspecific projection field unrelated to olfaction as a specific sense modality. Only the corticomedial amygdaloid complex and the medial portion of the basal nucleus, where the olfactory responses have a short latency of about 3 to 5 msec. and where no overlap with other modalities occurs, can be regarded as part of the specific olfactory receiving area (120).

With microelectrodes, evoked unitary discharges in response to electrical stimulation of the olfactory bulb are found in all subdivisions of the amygdala, except for the cortical and medial nuclei, usually considered to be part of the primary olfactory receiving area (166). The general characteristics of these unitary responses are similar to those evoked by other sensory stimuli to be discussed below (p. 1398).

With natural olfactory stimuli a rapid rhythm at 12 to 20 cps or even faster with a tendency to occur in spindles can be evoked in the piriform cortex and amygdala (4, 6, 38, 39, 59, 103, 172, 173). It is uncertain, however, whether this activity is specific for olfaction since it has been observed to occur in response to other sensory stimuli (173), to stimulation of the mesencephalic reticular formation (59) or even to stimulation of the anterior limbic cortex (133).[2]

In view of these anatomical and electrophysiological observations, there can be no doubt that the amygdala receives an important olfactory inflow. Yet the importance of the amygdala for olfaction as a sensory function still remains uncertain. Anatomical observations suggest that the amygdala cannot be very closely related to the olfactory sense since completely anosmatic aquatic mammals, like the dolphin or the porpoise, possess a very well-developed amygdala in which not even the corticomedial complex shows any signs of regression, except for the nucleus of the lateral olfactory tract, and yet there is no trace of an olfactory bulb, tract or prepiriform cortex (1, 30, 156). Furthermore in human brains with agenesis of the olfactory lobes the amygdala appears well developed (54).

This anatomical evidence is supported by physiological observations. Rats (238) and dogs (5) with bilateral destruction of the amygdala still retain the faculty of olfactory discrimination. Allen (5) found that the discrimination between a positive and a negative olfactory conditioned response was lost in dogs with bilateral amygdaloid-piriform lesions. However, in view of more recent evidence stressing the importance of the amygdala in conditioned avoidance behavior (see p. 1411), these results may have to be reinterpreted. They may indicate interference with the motivational forces involved in the particular conditioning procedure used rather than a true disturbance of olfactory discrimination.

Conflicting evidence regarding the olfactory function of the amygdala is given by human observations. Some authors (84) found a marked increase in olfactory threshold on the operated side after temporal lobectomy including the amygdala, whereas others (227) noted no such deficits.

Stimulation studies add little to the problem of olfactory functions of the amygdala. It is noteworthy that in man olfactory sensation is far less often produced by amygdaloid stimulation than other sensory experiences (129) (see page 1398). In animals, sniffing may be produced by amygdaloid stimulation (87, 135, 155, 172); but this response has to be considered within the context of other behavioral stimulation effects and is not necessarily evidence for primary olfactory representation in the amygdala.

OTHER AFFERENT SENSORY CONNECTIONS OF AMYGDALA. There is no convincing anatomical evidence for the presence of nonolfactory sensory afferent connections to the amygdala, although they have

[2] These findings are at variance with those of Carreras *et al.* (38) who found this response to be specifically olfactory. In their experiments it could not be elicited by other stimuli which produced only a low-voltage desynchronization of the electrogram as is typical for neocortical arousal.

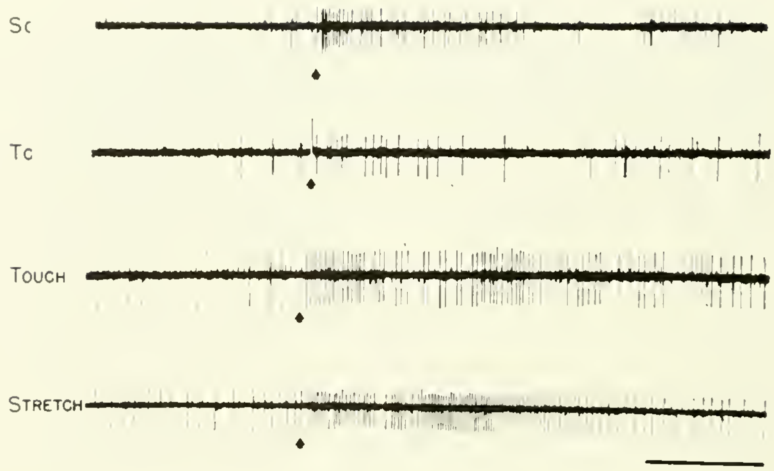

FIG. 2. Nerve cell discharges in the central nucleus of the amygdala evoked by single shock stimulation of the contralateral sciatic nerve (*Sc*) and of the tooth pulp (*Tc*) and by natural somatosensory stimuli, such as light touch of the fur of the contralateral hind leg and stretching of the gastrocnemius muscle. [From Machne & Segundo (166).]

been demonstrated electrophysiologically. Some anatomists describe thalamoamygdaloid fibers but their statements do not seem to be well documented (118, 177, 184).

Physiological studies, however, show that evoked potentials to all sensory modalities can be elicited in the amygdala (52, 53, 90, 166, 211). For classical evoked potentials the latency of these responses may vary from 8 to 25 msec. (52) and for unitary discharges may even measure anywhere from 20 to 500 msec. (166). This suggests mediation over long polysynaptic pathways. With the classic evoked-potential technique, responses to stimulation of the vagus and lingual nerves were most prominent (52, 53, 172); but unitary discharges recorded with microelectrodes seemed to be fired most effectively by somatic sensory stimuli, especially by a very slight touch to the skin (fig. 2) (166). These responses were mostly recorded from the basolateral complex. Responses to auditory and visual stimuli and to stimulation of the tooth pulp, presumably eliciting pain, were more difficult to obtain and more scattered in their distribution (52, 53, 166). Impulses originating from widely distant areas of the body surface, as well as impulses evoked by stimuli of different sensory modalities, were found to converge upon one and the same amygdaloid cell. The most frequent type of convergence was that of olfactory and somatosensory signals. Thus there is no topographical representation of sensory modalities or local areas of the body. The specificity of the sensory message is probably lost in this system, unless a specific temporal pattern of unitary discharge may serve as a code assuring its retention, a possibility suggested by some of the reported findings. Units were either directly fired in response to stimulus or they were activated in their spontaneous discharge pattern (fig. 2); more rarely, they were inhibited. Sometimes the response consisted merely of a shift in pace of the unit firing.

In view of their extensive overlapping these sensory evoked responses, including the olfactory ones, are probably unrelated to specific perceptual mechanisms as such (52). It is therefore of interest to recall at this point that the secondary sensory response of Forbes and Morison, most likely an unspecific sensory message, seems to be transmitted to the cortex via a region close to the temporal horn of the lateral ventricle, in which the most significant structure is the anterior pole of the amygdala (189).

Stimulation studies in man give additional evidence that the amygdala is involved in sensory functions (129). Patients in whom the amygdaloid region was stimulated frequently reported sensory experiences of ill-defined quality. The sensation was often referred to the body as a whole or to some part of it such as the head, the abdomen or even the extremities. Some animal studies also suggest that amygdaloid stimulation may evoke sensations, for instance when a cat upon amygdaloid stimulation fixes its gaze on a particular spot of its body and then proceeds to sniff and lick it intensely, or when the contralateral paws are lifted from the floor as if to remove them from an unpleasant contact (82, 135).

NONSENSORY AFFERENT CONNECTIONS TO AMYGDALA. A few other afferent connections to the amygdala have been described. Some of them are controversial from an anatomical point of view and so far unproved electrophysiologically, such as those from the mid-line and intralaminar nuclei of the thalamus (165, 203, 204, 215).

Other subcortical structures sending afferent connections to the amygdala are the reticular formation of the brain stem (166) and the striatum (132). The

former connections have been demonstrated by electrophysiological means, the latter by anatomical methods.

Several rhinencephalic connections are sources of afferent fibers to the amygdala, among them the tuberculum olfactorium (118, 122, 137, 157, 206), the piriform cortex, especially its anterior part (62, 109, 118, 132, 137, 153, 164, 184, 206, 207, 239, 247), and the hippocampus (104). The existence of these connections has been demonstrated by anatomical and electrophysiological methods, except for those from the hippocampus for which so far there is only electrographic evidence.

Finally there are neocortical afferent connections to the amygdala. Their anatomical description is still incomplete (132, 139, 163), but physiological studies have demonstrated the existence of pathways from the temporal pole, the first temporal convolution, the anterior insula, the posterior orbital cortex and from the motor area to the amygdala (121, 206, 207, 229). Differential effects upon the amygdaloid responses were noted on stimulation at a rate of 4 to 8 cps of the temporal pole and of the first temporal convolution. The former facilitated whereas the latter inhibited the evoked amygdaloid responses (229).

Efferent Connections

ANATOMICAL STUDIES. *Subcortical connections*[3]. There are two main efferent subcortical fiber systems of the amygdala: a dorsal one, the stria terminalis, swinging around the bulk of the internal capsule, and a ventral one, passing underneath it (see below). Of these pathways the best known is the stria terminalis of which several components have been described (26, 62, 63, 108, 109, 122, 137, 233, 256). The pattern of origin of this bundle from the amygdaloid complex is not clearly established.

The stria terminalis fibers end in the septal area, the preoptic region and the hypothalamus. Descriptions of the detailed pattern of their termination among the preoptic and hypothalamic nuclei are somewhat contradictory. It seems established however that the septal and preoptic area, the anterior hypothalamus and the ventromedial hypothalamic nucleus are the principal receptors of stria terminalis fibers. However, connections to all other hypothalamic areas and nuclei as far back as the premammillary region have been described by some investigators and denied by others (3, 21, 28, 108, 137).

[3] A vast anatomical literature exists on this subject which cannot possibly be reviewed in detail here. For fuller information consult the references listed in footnote 1.

Our anatomical knowledge of the ventral amygdalosubcortical pathways is less precise. Some of the fibers travel with the diagonal band of Broca and end in the tuberculum olfactorium and in the septum (118, 132, 137, 157), with some fibers entering perhaps the median forebrain bundle (109). Other fibers of this system have a less well-defined course (62, 63, 69, 122, 132, 157, 162, 233), some of them forming a rather diffuse system (62, 132), others being assembled into a bundle homologous with the ventral olfactory projection tract of lower forms (157, 162), and still others being associated with the longitudinal association bundle (62, 63) or even with the anterior commissure (122). These ventral fibers end in the bed nucleus of the stria terminalis, the septal and preoptic region, and in the anterior hypothalamus. Their projection territory therefore overlaps widely with that of the stria terminalis. Some fibers may connect with the entopeduncular nucleus (62), the subthalamus (162) or may even descend to the brain-stem tegmentum (162). There probably exist also some connections from the amygdala to the basal ganglia, especially to the putamen and claustrum (109).

Amygdalothalamic fibers have been described by some anatomists (64, 118), but their existence has also been denied (31). These fibers supposedly end in the pulvinar, the dorsomedial, lateralis posterior and lateralis dorsalis nuclei of the thalamus (64).

ANATOMICAL STUDIES. *Cortical connections.* Amygdaloid connections to the cortex are not well known anatomically. Most firmly established are the connections from the basolateral amygdaloid complex to the piriform cortex (47, 109, 132, 157, 184).

Amygdalohippocampal connections are described in normal material by some authors (69, 109, 118, 132, 162, 184); but others, on the basis of careful histological work including the use of experimental techniques, come to the conclusion that no direct amygdalohippocampal connections exist (3, 7, 31).

Still less is known about possible connections to other cortical areas. Some evidence has been cited that the cingulum (118), the tip of the temporal lobe (139) and the insula (163) may receive amygdaloid fibers.

ELECTROPHYSIOLOGICAL STUDIES OF EFFERENT AMYGDALOID CONNECTIONS. The anatomical findings concerning the efferent projections of the amygdaloid complex have been essentially confirmed and enlarged by electrophysiological studies in which evoked responses to single shock and repetitive amygdaloid

stimulation were mapped out in subcortical and cortical structures (96).

In confirmation of anatomical data it was found that the subcortical projection areas of the basolateral and the corticomedial subdivision of the amygdala overlap widely and that the efferent fibers, as judged by latency measurements, end in the basal septal region, the base of the head of the caudate nucleus, the preoptic area, the anterior hypothalamus and in the region of the ventromedial hypothalamic nucleus, the latter receiving direct fibers probably from the corticomedial complex only. The subcortical area, from which responses to amygdaloid stimulation were recorded, was however much larger than this 'primary projection field' and extended back to the mesencephalic tegmentum, including the remainder of the hypothalamus, the subthalamus, the entopeduncular nucleus and a small, essentially anteroventral part of the diffuse thalamic projection system (see also p. 1401). The responses recorded in this 'secondary projection field' are relayed from the 'primary' area over polysynaptic neuronal links, as indicated by the rapid and progressive increase of response latency as the recording electrode is moved away from the 'primary projection field.'

The two main subdivisions of the amygdala appear to discharge into the subcortex over two distinctly different fiber systems. Only the corticomedial complex seems to give origin to stria terminalis fibers since only in response to stimulation of this part of the amygdala were short-latency responses recorded in the stria terminalis. Responses from the basolateral

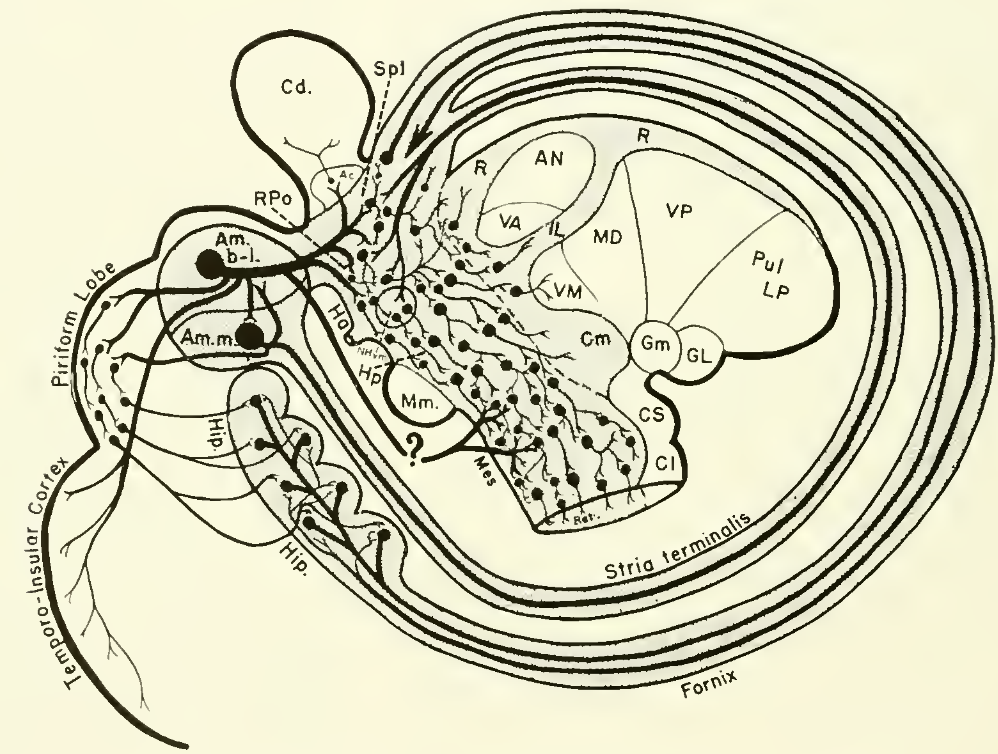

FIG. 3. Diagram of the neuronal organization of the amygdaloid projection system as revealed by electrophysiological studies. *Ac*, nucleus accumbens; *Am. b-l.*, basolateral subdivision of amygdala; *Am.m.*, corticomedial subdivision of the amygdala; *AN*, anterior thalamic nuclei; *Cd.*, caudate nucleus; *Cl*, inferior colliculus; *Cm*, centre médian; *CS*, superior colliculus; *GL*, lateral geniculate body; *Gm*, medial geniculate body; *Ha*, anterior hypothalamus; *Hip.*, hippocampus; *Hp*, posterior hypothalamus; *IL*, intralaminar nuclei of thalamus; *LP*, nucleus lateralis posterior thalami; *MD*, nucleus medialis dorsalis thalami; *Mes*, mesencephalon; *Mm.*, mammillary body; *NHvm*, nucleus ventromedialis hypothalami; *Pul*, pulvinar; *R*, nucleus reticularis thalami; *Ret*, reticular formation; *RPo*, regio preoptica; *Spt*, septum; and *Va*, nucleus ventralis anterior thalami. The *dotted area* represents the subcortical integrative areas regulating 'global' mechanisms and the limbic structures projecting into it. [From Gloor (96).]

complex may be transmitted over the stria terminalis as well but with latencies so long as to indicate that they are synaptically relayed in the corticomedial nuclei. This would presuppose the existence of an intraamygdaloid association system with short axons, a postulate supported by anatomical findings of various workers (62, 63, 118, 132, 154; Crosby, personal communication). Direct subcortical connections from the basolateral complex seem to be identical with the ventral amygdalosubcortical pathways described by the anatomists (see p. 1400).

Direct connections from the amygdala to the mesencephalic tegmentum may also exist in addition to those relayed over polysynaptic hypothalamic relays of the 'secondary projection field' since some shorter latency responses ranging between 10 and 15 msec. reappeared behind the posterior hypothalamus where the latencies measured between 15 and 25 msec. or even more. It is therefore possible that a direct amygdalomesencephalic pathway, such as is known to be present in birds (43, 55, 107, 112) and reptiles (137), may also exist in mammals where so far only scanty evidence for its existence could be derived from some physiological observations (250) and from some histological findings in marsupials (162).

The cortical projection field of the amygdala is rather restricted. Short-latency responses were recorded from the piriform, anterior temporal and insular cortex. An important but polysynaptic pathway relays from the amygdala to the hippocampus. It involves several synapses, presumably in the piriform cortex, as suggested by the long latencies of the hippocampal responses to amygdaloid stimulation which often exceeded 20 msec. The hippocampal responses mediated over this pathway may become very large with repetitive stimulation, as will be further described below, suggesting that this connection, although indirect, may be quite important functionally, a view also expressed by Crosby (personal communication) on the basis of anatomical studies.

This analysis of the neuronal organization of the amygdaloid projection systems reveals a very intimate relationship of the amygdala with highly integrative subcortical structures (fig. 3). This relationship is not a simple one; divergent paths from the amygdala converge again upon common neuronal pools, as evidenced by the existence of direct and indirect amygdaloseptal, amygdalohypothalamic and amygdalomesencephalic pathways. Some of the indirect pathways relay impulses through short intraamygdaloid connections. Thus impulses from the basolateral complex may be conducted to the stria terminalis via the corticomedial nuclei and, finally, both the direct and indirect systems converge upon the same septohypothalamic zone. In addition there is still a third possible route with polysynaptic relays via the piriform cortex to the hippocampus which in its turn discharges into the same general septohypothalamic zone by way of the fornix. This arrangement, together with the polysynaptic organization of the subcortical system upon which these pathways project, creates favorable conditions for a very flexible play of excitatory processes.

This flexibility is clearly revealed when repetitive electrical stimulation of the amygdala is applied to the study of its projection system (97). With relatively low-frequency (10 to 50 cps) repetitive stimulation the following changes of excitability were observed.

a) Recruitment, i.e. a gradual increase in the amplitude of the evoked response during repetitive stimulation (fig. 4), was ordinarily seen but occasionally the opposite phenomenon, a gradual decrease of the amplitude of the response, for which the term obliteration was used, appeared.

b) Potentiation, i.e. a state of residual facilitation outlasting the period of 'tetanic' repetitive stimulation to which it is due, manifests itself by an increased amplitude of 'posttetanic' single shock responses as compared to 'pretetanic' single shock responses (fig. 4).

c) Latency changes may be observed, either decreases or increases occurring without any constant correlation with the type of amplitude change.

These three types of changes were, as a rule, more prominent the longer the latency of the response; in other words, increase in the number of synaptic passages seems to amplify the excitatory changes conditioned by repetitive stimulation. Recruitment and latency changes were absent in the 'primary projection field' and potentiation here was minimal.[4] On the other hand, such changes were rather prominent in the 'secondary projection field' and were most conspicuous in the hippocampus where the longest latency responses were found. The short latency neocortical responses in the 'temporoinsular' cortex showed none of these changes.

[4] There is evidence however that a certain degree of potentiation already occurs at the actual site of stimulation in the amygdala. This contention is based on observations that the utilization time shortens after repetitive amygdaloid stimulation. Thus previously ineffective short pulses may be rendered effective in the posttetanic phase following a sequence of repetitive stimuli of long pulse duration (97).

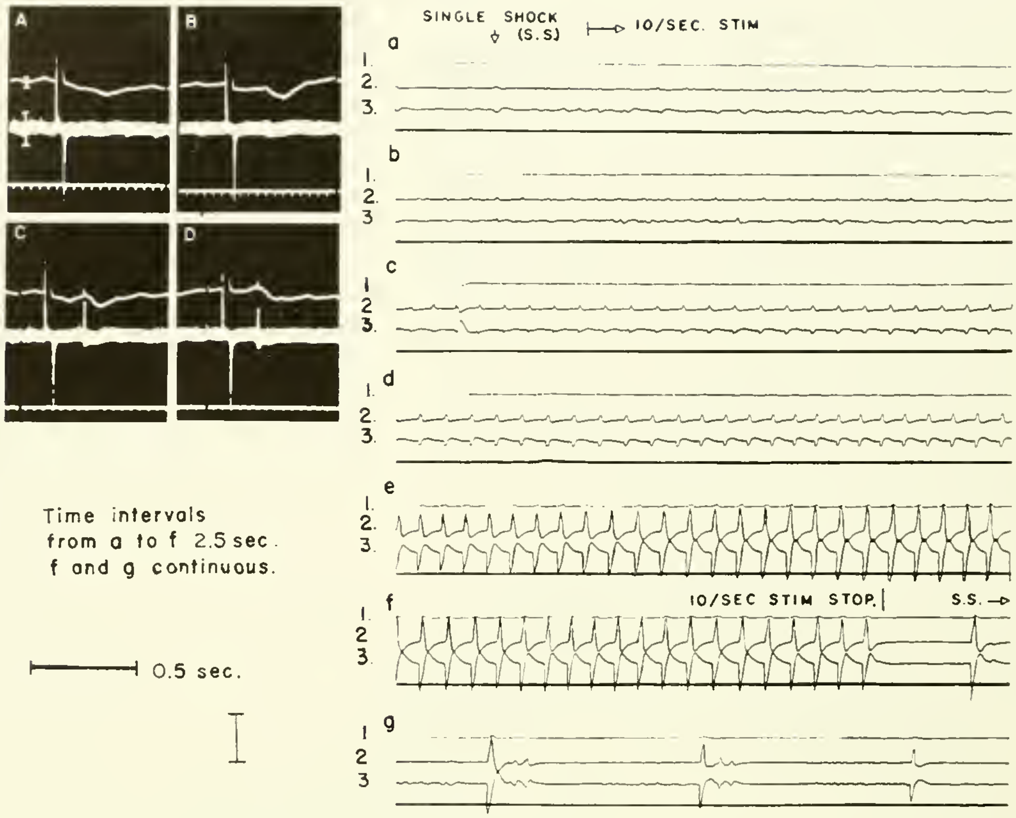

FIG. 4. Hippocampal responses to amygdaloid stimulation in the cat showing clear recruitment and potentiation. *a* to *g:* Bipolar records taken with a horizontal row of four electrodes inserted in a frontal plane into the portion of the hippocampus where it overlies the pulvinar thalami. *Channel 1:* Record from electrodes 1 and 2 located in the pulvinar where it is covered by the hippocampus. *Channel 2:* Record from electrodes 2 and 3, with electrode 2 in the pulvinar and 3 in the hippocampus. *Channel 3:* Record from electrodes 3 and 4 located in the hippocampus. No responses from the pulvinar. Gradual build-up of a high-voltage response in the hippocampus in response to 10 cps repetitive amygdaloid stimulation. The amplitude of the single-shock response, which is barely visible at this gain, is increased more than 10 times at the end of the period of repetitive stimulation. On resumption of 1 cps single-shock stimulation the response shows clear potentiation. The *insets A* to *D* in the *upper left* show sequences of the same phenomena recorded with a microelectrode. The tip of the microelectrode lies in the pyramidal layer of the hippocampus. Both *tracings* are from the same microelectrode, the *upper one* taken with a long time constant, the *lower one* at a higher gain with an ultrashort time constant. *A:* Single-shock response; small positive response, no unit spikes. *B:* After 2.8 sec. of 12 cps amygdaloid stimulation, showing augmentation of the amplitude of the positive response ('recruitment'), still no unit spike discharge. *C:* 11 sec. later during 12 cps repetitive amygdaloid stimulation; pyramidal cell recruited into firing as evidenced by unit spike discharging on top of a negative deflection which has developed in the trough of the initial positive response. *D:* Second posttetanic potentiated response; unit fired as in *C*. Calibration for *a* to *g*, 5000 μv; for *A* to *D*, 250 μv. Time scale in *A* to *D*, 10 msec. [Modified from Gloor (97, 101).]

In the hippocampus the different aspects of these excitatory processes were most consistent with each other (fig. 4); prominent, slow and gradual recruitment was followed by marked potentiation and this was often associated with a decrease in latency. In other parts of the amygdaloid projection system, however, these different excitatory changes were often dissociated; for instance, in the ventromedial hypothalamic nucleus where recruitment was absent or minimal, potentiation was very prominent; again, in the upper brain stem and in the piriform cortex, recruitment was often associated with a seemingly paradoxical increase of the response latency.

Some of the discrete neuronal mechanisms under-

lying these changes were recently investigated more thoroughly with microelectrode techniques (98). Recruitment and potentiation occurring in response to amygdaloid stimulation were studied in the hippocampus. It was found that the excitatory changes underlying recruitment and potentiation take place in the layer of the long apical dendrites of the hippocampal pyramidal cells since the maximum negative wave or 'sink' of the response was localized in the dendritic layer. The slow dendritic response to single shock often was not associated with propagated discharge from the pyramidal cells. A progressive build-up of the dendritic excitatory state was required to enable the pyramidal cell to fire off action potentials. This was signaled by the appearance of unit spikes riding on the crest of a negative deflection within the trough of the positive wave which was the electrical sign of the evoked dendritic response when recorded from within the cell layer (fig. 4*A* to *D*).

Since these excitatory changes are most prominent with polysynaptic responses, it is probable that this modulating dendritic mechansim may operate at successive synaptic junctions, thus amplifying the effects with each synaptic passage. Some of these synaptic way stations may actually be present within the intraamygdaloid association system since it was observed that the stria terminalis response may become quite complex under the influence of repetitive amygdaloid stimulation. It is thus apparent that the rate of amygdaloid firing is capable of regulating the mode of transmission of the responses in a very large degree. Certain synaptic barriers are not transgressed under certain conditions, but under others facilitatory processes may build up to open these synaptic barriers.

The mechanisms underlying the changes in latency still remain unclear. Decrease in latency may be due in some cases to shortening of synaptic delays due to the facilitatory effect of dendritic depolarization. In other cases latency changes may be due to differential facilitatory effects within vicarious routes involving a greater or smaller number of synaptic stations. If the excitatory changes induced by repetitive stimulation favor conduction over the shorter pathways, the latency will decrease; if, on the contrary, facilitation occurs predominantly in more involved pathways, then the latency will increase and yet the response will recruit.

Commissural Connections

Fibers of the anterior commissure connect the amygdala with its fellow on the contralateral side. These fibers enter the commissure directly, except for those forming the commissural component of the stria terminalis which run with this bundle first until it crosses the anterior commissure (26, 66, 109, 122, 130, 132, 233). The amygdaloid fibers taking a direct course into the anterior commissure were for a long time believed to originate from the basolateral amygdala (118, 122, 130, 157, 256), but more recently Brodal (33) has demonstrated that they originate in the corticomedial complex. No detailed electrophysiological studies on these commissural connections have so far been reported.

ELECTRICAL ACTIVITY OF AMYGDALA

The spontaneous amygdaloid electrogram in cats shows irregular 4 to 6 cps rhythms of 100 to 200 μv amplitude (103). Often rapid spindles at 16 to 26 cps are seen which tend to be synchronous with the respiratory rhythm, are usually arrested by blocking of the nasal airway and are enhanced by olfactory (103, 172) or reticular (59) stimulation. This activation may therefore represent the arousal pattern of the amygdala (see footnote on p. 1397). Other studies (20) however revealed no change in the amygdaloid electrogram upon reticular stimulation. Some observers (158) recorded spontaneous spike discharges from the amygdala, but it seems that this must be interpreted as an injury discharge (102).

STIMULATION STUDIES

Excitability

Electrical stimulation of the amygdala and the neighboring cortex shows that this region is electrically highly excitable. Stimulation responses as well as seizure discharges are elicited at a threshold which is generally lower than that in other parts of the brain, except for the hippocampus (93, 133, 160, 175, 190).

Electrocorticographic Responses

Electrical stimulation of the amygdala is apt to produce diffuse flattening of the cortical electrogram together with an increase in background frequency and asynchrony (20, 59–61, 133). Simultaneously, barbiturate spindle bursts, slow waves and epileptiform spikes, including those evoked by a weak strychnine solution may be suppressed. These

electrocorticographic responses are in all points similar, if not identical, with the 'arousal response' as elicited by stimulation of the brain-stem reticular formation (59). Furthermore the amygdaloid 'arousal' pattern with activation of the fast spindles (see p. 1403) can be elicited in one amygdala by stimulating the contralateral amygdala. These observations suggest a close relationship of the amygdaloid complex with subcortical regions exerting diffuse regulatory effects upon the electrical activity of the cortex.

Effects upon Spontaneous or Evoked Somatomotor Activities

Spontaneous movements going on at the time of onset of amygdaloid stimulation are usually arrested thereby. Thus in anesthetized preparations shivering, struggling and spontaneous chloralose-jerks are inhibited and there is concomitant reduction in muscle tone (133, 135). In unanesthetized animals this 'arrest' reaction assumes the form of a sudden cessation of motor activities in which the animal is engaged at the time of onset of stimulation. In the awake animal there is usually no decrease but an increase in muscle tone when this 'arrest' reaction occurs (72, 133, 172, 190, 245).

Spinal reflexes and cortically evoked movements are facilitated or inhibited (fig. 5A) by amygdaloid stimulation (133). Points producing facilitation and those eliciting inhibition are not clearly separated but overlap extensively.

Motor Responses

In awake freely moving animals a variety of tonic movements can be elicited by stimulation of the amygdala. The most frequent response is contraversive turning of the head and eyes, sometimes together with rotation inducing a posture as if the animal were looking backward over its shoulder. More rarely, vertical head movements are seen. If stimulation is maintained, the animal may be induced to circle around or to roll over on its side (11, 13, 22, 73, 87, 88, 133, 135, 155, 175, 190, 245).

Sometimes postural movements of the extremities are elicited. They usually involve flexion of the contralateral and extension of the ipsilateral limbs (135). Similar tonic movements are also observed in man (61, 129).

Clonic rhythmic movements are sometimes induced by amygdaloid stimulation. Most often these involve the ipsilateral face[5] (11, 13, 22, 23, 72, 73, 87, 152, 172, 175, 190, 239, 245); more rarely, the extremities (87, 135).

Complex rhythmic movements related to eating, such as licking, chewing and swallowing, are frequently observed upon amygdaloid stimulation. Often a latent period of 5 to 20 sec. elapses between the onset of stimulation and their appearance (11, 13, 22, 72, 73, 87, 88, 129, 133, 135, 172, 175, 186, 190, 209, 239, 245). In some instances these 'masticatory' movements assume a different character and the animal acts as if trying to disgorge a foreign body or something distasteful. This often leads to gagging and retching, but seldom to true vomiting (72, 73, 87, 172, 190, 245).

Rarely, vocalization occurs upon stimulation of the amygdala (72, 168, 172, 190, 245).

Vegetative Responses

Respiratory changes are very frequently elicited by amygdaloid stimulation. These may affect all physical characteristics of respiration, such as rhythm, amplitude and rest position of the thorax (72). The most frequent response is inhibition of respiration (fig. 5A) affecting both rhythm and amplitude (11, 12, 72, 88, 133, 135, 160, 172, 201, 245). Often there is respiratory arrest with escape 25 to 60 sec. later. Acceleration of respiration (fig. 5*B*), with increased or decreased amplitude, often preceded by a short period of apnea, is less frequently seen (12, 72, 88, 146, 147, 172, 190). Specific modifications of respiration, such as sniffing, sneezing and coughing, are also sometimes produced (72, 88, 133, 155, 175, 190).

Various cardiovascular responses occur upon amygdaloid stimulation (11, 12, 22, 41, 72, 88, 149, 168, 172, 188, 190, 201). Both increase and decrease in arterial pressure and more rarely, acceleration or slowing of the heart beat can be produced. Changes in heart rate do not show any consistent relationship with the direction of the arterial pressure response (12).

Gastrointestinal motility and secretion can be inhibited (fig. 5*D*) or activated by amygdaloid stimulation (11, 15, 56, 149, 150). Defecation (fig. 6) and even more frequently micturition may be induced,

[5] Since these movements often appear only after some latent period, do not follow the frequency of the applied electrical stimuli, may outlast the end of the stimulation and cannot be reproduced by stimulation of adjacent parts of the brain or the dura covering the middle fossa, they cannot be attributed to spread of current to the facial nerve.

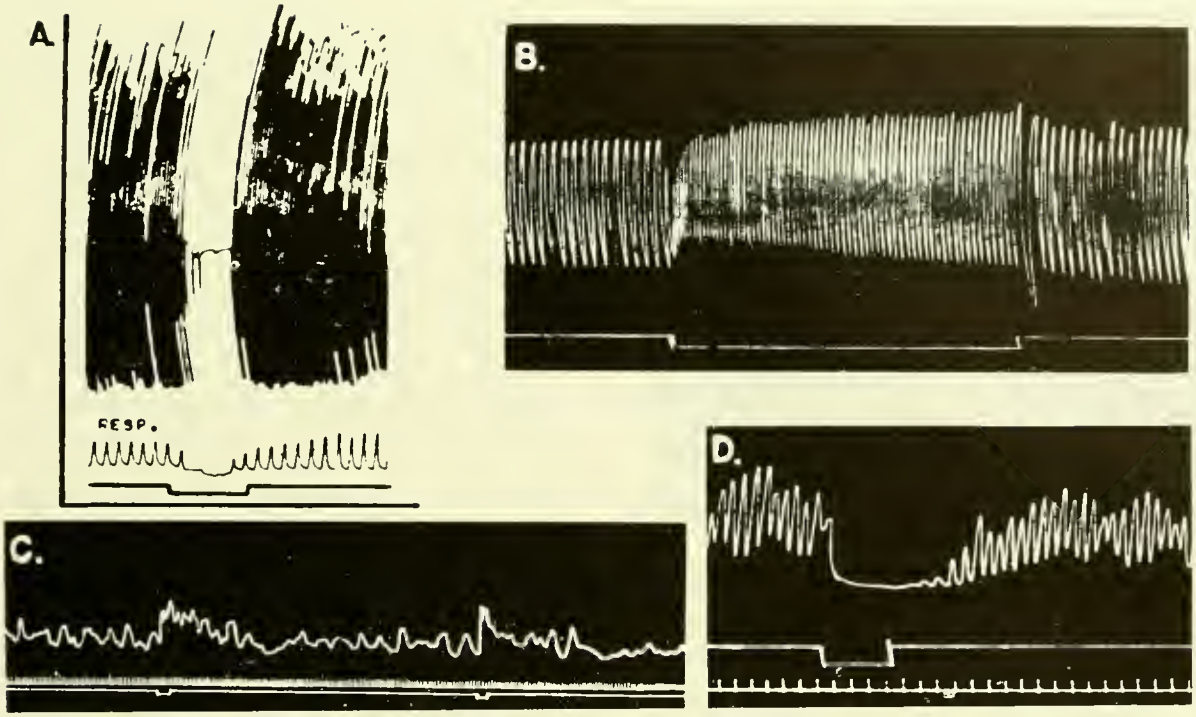

FIG. 5. Examples of various amygdaloid stimulation responses. *A:* Inhibition of the knee jerk elicited every 2 sec. (*upper tracing*) and of respiration (*lower tracing*) in the cat. [From Kaada (133).] *B:* Activation of respiration by amygdaloid stimulation in the cat. [From Koikegami & Fuse (146).] *C:* Increase in uterine tonus and contractions followed by a short phase of inhibition in response to amygdaloid stimulation in the rabbit. [From Koikegami *et al.* (151).] *D:* Inhibition of activity of small intestine produced by amygdaloid stimulation in the cat. [From Koikegami *et al.* (149).]

and often the animal assumes its habitual posture to perform these acts (11, 72, 82, 87, 88, 133, 135, 168, 172, 175, 190, 245).

Amygdaloid stimulation also influences uterine tone and contractions (fig. 5*C*). The response is diphasic, with an initial period of activation followed by inhibition, and is most marked during estrus and feeble during the luteal phase and early pregnancy (151).

Pupillary dilatation is often elicited with retraction of the nictitating membrane and slight exophthalmus (11, 13, 41, 72, 133, 135, 152, 168, 172, 175, 190, 209, 239, 245). More rarely pupillary constriction is seen (13, 152, 172) or dilatation interrupted by an interim period of constriction (72).

Other vegetative responses reported are piloerection (72, 135, 168, 172, 175, 190, 245), secretion of a thick sympathetic type of saliva (fig. 6) or, more rarely, of a thin parasympathetic type (11, 13, 22, 72, 73, 87, 135, 148, 155, 168, 172, 190, 209, 239, 245), and also secretion of the lacrymal and nasal glands (11, 13, 22, 72, 73, 155, 168, 172, 175, 190).

Finally, it has been claimed that amygdaloid stimulation may influence the body temperature so as to produce an initial drop of about 1 °C for 40 to 45 min., followed after 3 to 8 hr. by a peak of temperature of about 2 °C above the initial value, with gradual return to normal in about 24 hr. (150). Unfortunately, the absence of adequate controls makes evaluation of these results difficult.

Endocrine Responses

In the female rabbit amygdaloid stimulation seems to elicit release of gonadotrophic hormone from the pituitary, as judged from the occurrence of ovulation (151, 221). This effect is said to occur very frequently during estrus and some response can even be obtained in the anestrus phase, as evidenced by the presence of enlarged and sometimes hemorrhagic follicles.

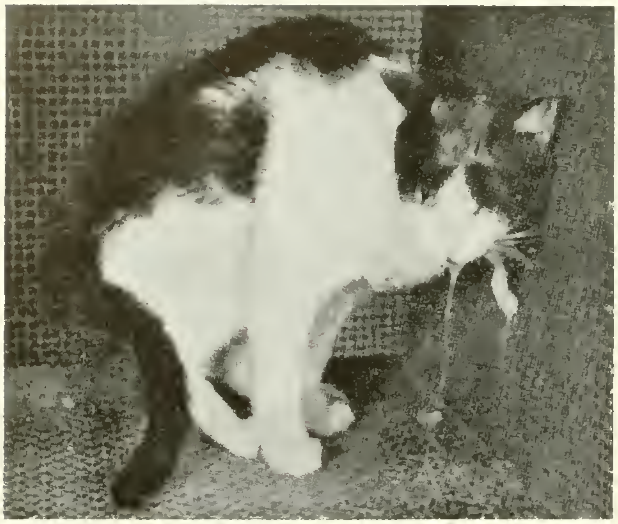

FIG. 6. Salivation and posture of defecation elicited by amygdaloid stimulation in the cat. [From Anand & Dua (13).]

Information in regard to other endocrine glands is scanty. An increase in blood sugar concentration is sometimes noted after amygdaloid stimulation and thought to be evidence for epinephrine discharge (11, 14). Occasionally the opposite is seen, suggesting activation of insulin secretion (14). Recently, Mason (178) has observed that amygdaloid stimulation produces unmistakable signs of ACTH release by the pituitary gland.

Integrated Behavioral Responses and Psychic Phenomena

FEEDING BEHAVIOR. Sniffing, often along the floor, together with searching movements are common effects of amygdaloid stimulation (11, 72, 87, 88, 133, 135, 155, 168, 172, 175, 190). Repeated short amygdaloid stimulations may induce increased nuzzling, sniffing and licking for one or several days (9). After amygdaloid stimulation, food is eaten avidly (72). However there seems to be no increase in the amount of food intake (11, 13, 50).

ATTENTION, FEAR AND RAGE. The most common behavioral responses elicited by stimulation of the amygdala are reactions of attention, fear and rage (11, 13, 51, 72, 82, 87, 88, 135, 155, 168, 172, 175, 186, 187, 190, 245), three types of behavior which apparently are closely interrelated since, upon increasing the intensity of stimulation, attention will merge into fear and finally lead to rage (72). In man, fear is occasionally, and rage only rarely elicited by amygdaloid stimulation (41, 111, 129). The attentive response is associated with arrest of ongoing behavior and with the usual somatomotor and autonomic changes attending a normal attentive response of the animal. The same principle holds for fear and rage which also are accompanied by the typical postural and autonomic changes correlated with these forms of behavior. The rage reaction may lead to an attack which may be well directed (172) or not (88).

Gastaut and co-workers (88) pointed out that the sequence of attention, fear and rage corresponds closely to Pavlov's (196) 'orienting reflex' and to its modifications occurring with increasing intensity of the alerting stimulus. The vegetative changes attending this Pavlovian orientation response are also quite similar to those observed on amygdaloid stimulation (210).

It seems worthy of note that on a few occasions amygdaloid stimulation in animals was seen to produce quite an opposite, quieting effect sometimes leading even to sleep (11, 13).

REWARDING EXPERIENCES. Amygdaloid stimulation in awake unrestrained rats may induce a behavior suggesting that such stimulation may produce an 'experience' which acts as a reward (192–194). This was seen in experiments in which rats were able to stimulate their own brain by pressing down a bar, thus closing the stimulation circuit connected to the electrodes implanted in the animal's brain. A delay switch turned off the stimulation after a few seconds and the animal had to release the bar and press down again to receive another stimulation. The time the animal spends bar-pressing serves as an index of the rewarding character of the stimulation. In such an experimental situation the amygdala, together with the septum, gives the highest scores, indicating that stimulation of these areas is experienced as a reward; this type of reward can even be used instead of food to improve the rat's performance in running through a runway.

SEXUAL BEHAVIOR. Occasionally behavioral responses suggesting sexual excitement may be observed in female cats upon amygdaloid stimulation (72).

MODIFICATIONS OF LEVEL OF AWARENESS, CONFUSION AND INTERFERENCE WITH MEMORY RECORDING MECHANISMS. Amygdaloid stimulation in man frequently produces confusion, disturbances of awareness, unresponsiveness and amnesia for all events taking

place during stimulation (41, 61, 129, 160, 198). This suggests that stimulation of the amygdala may easily interfere with memory-recording mechanisms and processes integrating conscious perception. Evidence that this is also the case in animals, although they may display the pantomime of attentive behavior, is given by Gastaut and his collaborators (72, 82, 88, 186, 190). An interesting observation is that lack of awareness in these animals is sometimes restricted to stimuli applied to the side of stimulation from which the head is turned due to the contraversive effect of stimulation less (88).

Topographical Representation of Function in Amygdala

Two groups of workers have tried to correlate specific amygdaloid stimulation responses with particular subdivisions of the amygdala. Kaada *et al.* (135) state that the autonomic and immediate somatomotor responses are obtained by stimulating the anteriomesial part, comprising the corticomedial complex and the medial portion of the basal nucleus. Stimulation of the lateral amygdala, comprising the lateral part of the basal nucleus and the lateral nucleus, is said to elicit behavioral responses such as attention, fear and rage and also responses suggestive of some subjective sensory experience. There was, however, a striking accumulation of autonomic, somatomotor and behavioral types of responses in the basal nucleus, the density of responsive points falling off rather rapidly both in the medial and lateral direction. The work of Koikegami and his collaborators (146–152) also shows that most of the responses were obtained from the basal nucleus. According to the results of Kaada *et al.* (133) only a small proportion of the autonomic and somatomotor responses were obtained from points clearly within the corticomedial subdivision. It may therefore not be significant that no behavioral responses were obtained from the corticomedial subdivision in this experimental series.

Koikegami and his collaborators (146–152) attribute to the medial portion of the basal nucleus predominantly sympathetic effects, and consider the lateral portion of the basal nucleus and the cortical and medial nuclei as activating parasympathetic functions.

Other authors have been more impressed by the wide range of overlap of points yielding a rich variety of responses and felt that no topographical organization of functions could be deduced from stimulation results (fig. 7) (11–15, 82, 172, 190). However, despite this hesitancy to attribute certain functions to certain definite amygdaloid subdivisions, many authors indicate the locations from which they obtained particular stimulation effects. A comparison of all these findings, as shown in table 1, fails however to reveal any consistency in localization of the various amygda-

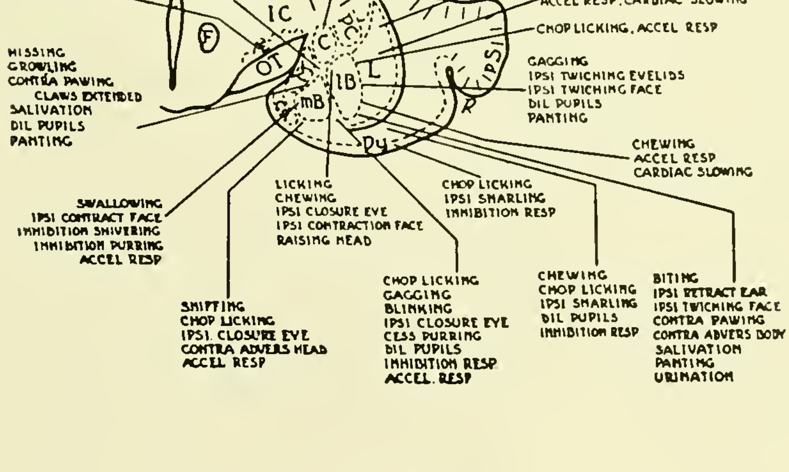

FIG. 7. Map of stimulation responses obtained from the amygdala. [From MacLean & Delgado (172).]

TABLE 1. *Amygdaloid Stimulation Responses Reported by Several Authors, Tabulated According to Localization of Responsive Areas Within the Amygdaloid Complex*

	Kaada (134)	Kaada *et al.* (136)	Naquet (190)	Gastaut (73) Morin *et al.* (188)	MacLean & Delgado (173)	Koikegami *et al.* (147–153)	Takahashi (238)	Baldwin *et al.* (22)	Baldwin *et al.* (23)	Anand & Dua (14)	Lammers & Magnus (156)	Magnus & Naquet (176)
Inhibition of spontaneous movements	More in M.	M.A.	More in L.		L.							
Effects on evoked motor activities												
Inhibition	More in M.											
Facilitation	More in L.											
Contraversion		M.A.	S.M.							M.A.	LN.	CN. AA.
Clonic facial movements			L.M.				BN.	S.M	L.L.			BN. CN. AA (EC. PC.)
Licking, chewing, swallowing		M.A.	L.	L.M			BN.					BN. CN. AA (EC. PC.)
Respiration												
Inhibition		M.A.	S.	LN BN.		LN						
Activation					AA.	BN.						
Blood pressure												
Rise			M	S.M.		BN. (lat. Pt)						
Fall			L.	L.		CMN.						
Pulse rate												
Rise	No precise localization given											
Fall					A.							
Gastrointestinal responses						BN. (med. Pt.) LN.						
Micturition and defecation		M.A.										MN. BN CN. AA.
Uterine movements						BN.						
Piloerection												M.A.
Pupils												
Dilatation		More in M.A.	M.			BN.						Whole Amygd.
Construction						BN. (lat.-ant.)						
Salivation		M.A.		L.M							BN.	BN. CN AA (EC. PC.)
Sympathetic						BN. (med. Pt)						
Parasympathetic						BN. (lat. Pt.) CN MN						
Nasal secretion											AA.	AA.
Ovulation						BN. (CN.)						
Body temperature						LN.						
Attention		L.			LN.							
Fear-Rage		L.	M							M.A.	M. AA.	M.A.
Sniffing		M.A. (LN. BN.)		L.A.M							BN.	BN. (lat. Pt.) LN. CN. AA.

loid stimulation responses. It therefore appears that the organization of function in the amygdala (and probably in other parts of the rhinencephalon) is of a different order than that typical of certain neocortical areas with their mosaic-like representation of specific separate functions (96, 99). Functional representation in the amygdala, and probably in other rhinencephalic structures as well, seems to be of a more global and topographically undifferentiated type. This would not exclude the possibility that the cytoarchitectonically defined subnuclei of the amygdala may have their specific tasks in amygdaloid function. It seems however that their contribution is not related to any particular types of amygdaloid responses but rather may contribute in some as yet unknown way to the elaboration of all functional effects obtained by amygdaloid stimulation.

Mediation of Amygdaloid Stimulation Responses

According to Koikegami and his collaborators (146–152) most vegetative responses, except respiratory and arterial pressure changes which depend upon the stria terminalis, are mediated via direct ventral amygdalohypothalamic pathways. However, there also is some evidence that respiratory changes may still occur after cutting of the stria terminalis (133) and that arterial pressure responses may even be elicited by direct influence upon the brain stem bypassing the hypothalamus (250).

Inhibition of spinal reflexes (133), mastication (115), sniffing, sneezing and coughing (116), micturition and defecation (114, 136) can also be elicited by stimulation of the stria terminalis or its bed nucleus. This suggests that this bundle takes part in mediating these responses, although it does not exclude the existence of alternative pathways.

The extensive projection of the amygdala upon subcortical structures as revealed by electrophysiological studies (96) explains how it is possible that such a confusingly great number of responses can be elicited by amygdaloid stimulation. Any response produced by stimulation of the amygdala is also known to be elicitable from stimulation of some other subcortical structure to which the amygdala projects. Figure 8 shows these relationships in a diagrammatic way. The work from the schools of Ranson, of Hess and of Magoun has demonstrated the highly integrative character of these subcortical structures and the topographical organization of function which prevails among them. Purposeful patterns of function made up of integrated component functions are elicited from definite areas to the exclusion of others. In the amygdala this type of organization seems to be absent. This is in accord with the fact that the amygdala is able to fire into various subcortical structures regulating different or even antagonistic functions. Thus it becomes understandable that the amygdala can influence one and the same function in opposite ways. Examples of this are numerous, such as facilitation and inhibition of evoked motor activities, inhibition and activation of respiration, rise and fall in arterial pressure, activation and inhibition of gastrointestinal function, and so forth.

Dynamic Aspects

Naquet (190) has drawn attention to some important dynamic aspects of amygdaloid stimulation responses. Stimulation in the unanesthetized animal shows that all the varied effects are not elicited simultaneously but appear in a patterned time sequence (fig. 10). The immediate effects are quite discrete and often merely consist of a slight change of the respiratory rhythm together with some mild attention response. If stimulation is maintained the delayed responses appear with a latency of 10 to 30 sec. They usually begin with acceleration of respiration, pupillary dilatation and sniffing, followed in sequence by some clouding of awareness, contraversion, ipsilateral facial clonus, licking, chewing and swallowing with salivation, and finally fearful behavior or micturition or defecation. This sequence of events may vary slightly, but once started it will generally outlast the end of stimulation with a local electrical after-discharge conducted to cortical and subcortical areas receiving amygdaloid connections.

The dynamic aspects of amygdaloid responses are also illustrated by Kaada's observations (133) that facilitation and inhibition of spinal reflexes and cortically induced movements exhibit 'recruitment' and may outlast the end of stimulation as does the local electrical after-discharge.

It thus appears that the recruiting phenomena shown by electrographic studies (97) have their counterpart in the mode of development of amygda-

A., anterior part of the amygdala; *A.A.*, anterior amygdaloid area; *B.N.*, basal nucleus; *C.M.N.*, corticomedial nuclei; *C.N.*, central nucleus; *EC.*, external capsule where it borders the lateral nucleus; *I.A.M.*, inferoanteromedial part of the amygdala; *I.L.*, inferolateral part of the amygdala; *I.M.*, inferomedial part of the amygdala; *L.*, lateral part of the amygdala; *L.N.*, lateral nucleus; *M.*, medial part of the amygdala; *M.A.*, medioanterior part of the amydgala; *M.N.*, medial nucleus; *PC.*, periamygdaloid cortex; *S.*, superior part of the amygdala; *S.M.*, superomedial part of the amygdala.

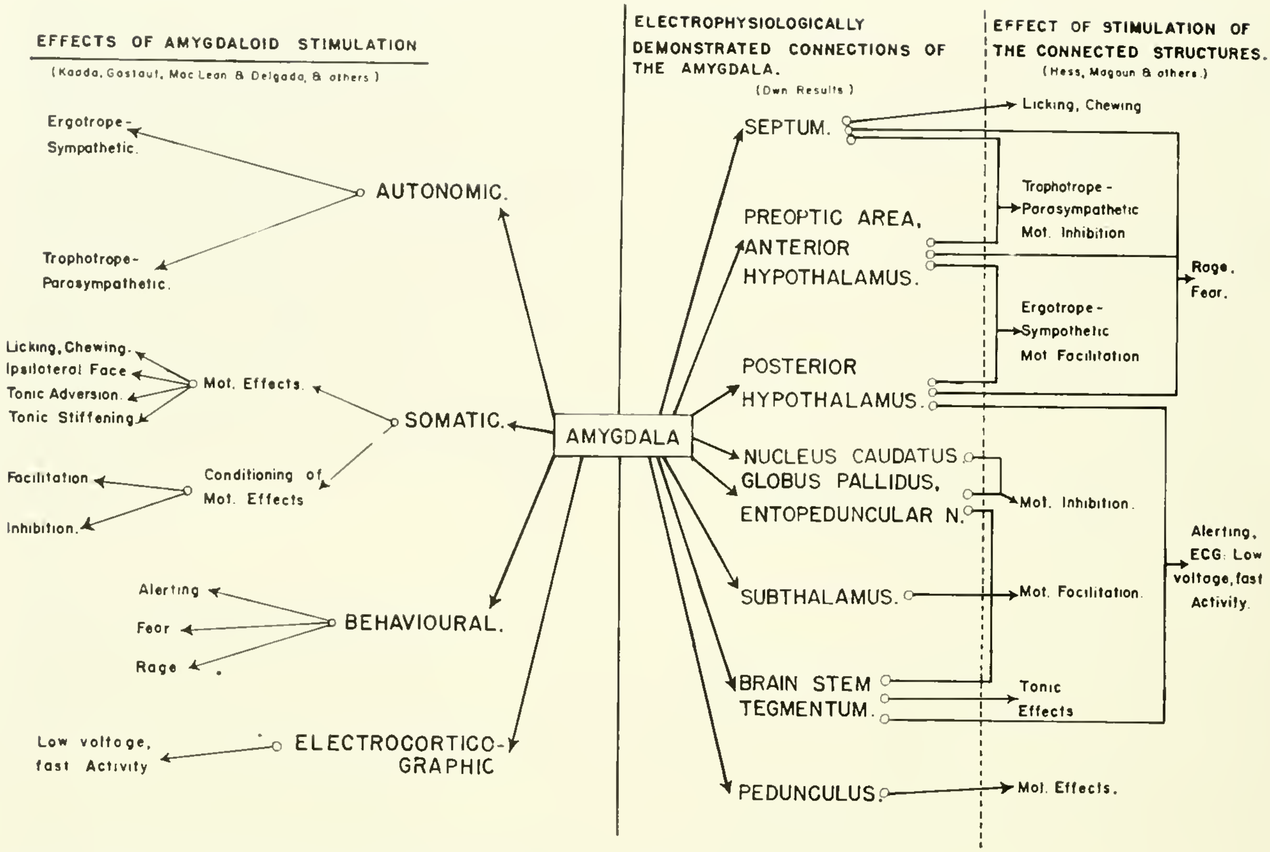

FIG. 8. Diagram illustrating the electrophysiologically demonstrated direct and indirect connections of the amygdala and their functional significance. On the *left hand side* are listed the responses to amygdaloid stimulation as described in the literature. The *middle column* lists the structures which on electrophysiological investigation were shown to be fired in a direct or indirect way from the amygdala. On the *right hand side* the responses obtained by stimulation of these structures as reported by Hess, Magoun and others are listed. Note that the responses obtained upon amygdaloid stimulation are also obtained from one or other of the subcortical structures to which the amygdala projects and that there is a topographical grouping of these effects in the subcortex, and that such a grouping is absent at the amygdaloid level. [From Gloor (96).]

loid responses. Neuronal recruitment at successive synaptic stations seems to induce a patterned sequence of responses together with a gradual increase in the intensity of certain responses. Furthermore it seems that clearly noticeable effects, resulting in overt somatomotor, vegetative or behavioral changes, only appear when there is after-discharge, i.e. seizure activity. All this concurs in suggesting that the amygdala is not in actual command of the various mechanisms which it is capable of influencing when electrically stimulated, but rather acts as a modulator of activities integrated at subcortical levels (97, 99).

[6] The only exception to this is the report by Koikegami *et al.* (148) stating that bats were no longer able to fly after amygdaloid lesions. Their wing-spreading reflex elicited by pinching their neck was also abolished on the side of the lesion.

LESION EXPERIMENTS

Amygdaloid lesions have to be bilateral to produce any detectable changes. The varied somatomotor[6] and autonomic mechanisms, so clearly influenced by amygdaloid stimulation, show only transient minor deficits or none at all after bilateral destruction of the amygdala. Such transient autonomic changes described include some tendency to increase in arterial pressure, decrease in heart and respiratory rates, some instability of blood sugar and blood sodium concentration, hyperemia and ulcerations of the gastrointestinal mucosa (16), increased salivation (148), piloerection (252) and slight hypothermia with relative poikilothermia (10, 148, 199, 204).

There is some evidence that endocrine changes

may result from amygdaloid lesions. Some authors (148) describe rather severe atrophic changes in the anterior pituitary, the thyroid, the adrenal cortex and the Langerhans cells of the pancreas, with consequent weight loss and growth deficiency, in puppies with bilateral amygdaloid lesions. Yet in adult animals no endocrine changes suggestive of such atrophic lesions were reported to occur following bilateral amygdalectomy. On the contrary, although the glycemic response to emotional stress is abolished after bilateral amygdaloid lesions (200), there is no evidence that such lesions affect the ACTH secretion in response to stress (16, 200; Guillemin, personal communication). There is however some, although not entirely unequivocal, evidence that amygdaloid lesions may produce an increase or imbalance in the secretion of gonadotrophic and sex hormones (142, 223, 224).

Transient disturbances in the sleep-wakefulness cycle with prolonged sleeplike states (199, 223, 227, 228, 240) as well as more persistent disturbances of a narcoleptic character (204) are sometimes observed after bilateral amygdaloid lesions.

All these changes are however insignificant when compared with the very dramatic alterations in behavior produced by bilateral amygdaloid lesions. These behavioral changes were first described in 1888 by Brown & Schäfer (35). They then fell into oblivion until rediscovered in 1937 by Klüver & Bucy (143). According to these authors (36, 140–145), the following syndrome develops in monkeys after bilateral anterior temporal lobectomy, including the amygdala: *a*) visual agnosia; *b*) hypermetamorphosis, a strong urge to attend and react to every visual stimulus; *c*) oral compulsive behavior; *d*) profound changes in emotional behavior with loss of fear and of aggressiveness; *e*) hypersexuality; *f*) changes in dietary habits with acceptance of meat as food; and *g*) increased and peculiar spontaneous motor activity.

Although the lesions in these monkeys included far more than the amygdaloid complex, most of these disturbances have since been described with more restricted anteromesial temporal lesions including little, if anything, more than the amygdala. Although from study of the effects of small temporal lobe lesions it appears that some aspects of the behavioral disturbances are more critically related to certain parts of the temporal lobe than to others, it is nevertheless not possible to arrive at a neat classification of behavioral components by assigning to each of them a well-defined anatomical localization. Obviously all these behavioral mechanisms are intimately interlocked and the full syndrome is more than the sum of individual deficits attributable to individual anatomical structures (141, 249).

Disturbances of emotional behavior are the most consistent results of such lesions and it seems that the amygdala is the structure, involvement of which is critical in the production of these emotional changes. Most frequently animals with such bilateral amygdaloid lesions become placid and display no reactions of fear, rage or aggression (10, 17, 29, 72, 187, 199, 200, 204, 217, 222–224, 234, 241, 245, 249, 252, 254). Not only is the rage threshold considerably increased, but prey is no longer attacked (223) and the 'social' integration of the individual within a group is greatly altered. Thus previously dominant individuals in a monkey colony become the outcasts, subjected to unremitting abuse against which they do not retaliate (218). These emotional changes are also reflected in alterations of conditioned avoidance behavior, including impairment of its acquisition in cats; its retention was however unaltered (29), a fact suggesting that amygdaloid lesions depress the motivational facilitation for the acquisition of conditioned avoidance. Somewhat different results were however obtained in monkeys (252) where acquisition was only slightly slowed, but extinction of a preoperatively acquired conditioned avoidance response became more rapid than in normal controls. Furthermore it seems that the motivational impact of frustration was also diminished.

Entirely opposite results to those so far reviewed were however reported by Spiegel *et al.* (236) and by Bard & Mountcastle (24) who found that bilateral amygdalectomy in cats transforms a placid animal into a savage beast reacting to the most trifling stimuli with an outburst of well-directed rage. The discrepancies of these findings with those previously summarized cannot be explained on the basis of a species difference since amygdalectomy in cats is also apt to produce placidity (186, 222–224). Schreiner & Kling (223, 224) attempt to explain this discrepancy by pointing out that amygdaloid lesions produce savage behavior in carnivores only after an initial period of docility and that aggressiveness reappears with the onset of increased sexual behavior. Since sexual excitement in carnivores is normally associated with combative behavior, the return to savageness may thus be part of the hypersexual syndrome, a view corroborated by their observation that subsequent castration will both abolish hypersexuality and restore docility. It should however be recalled that the cats in the experiments of Spiegel

et al. (236) were savage immediately after the operation and that Bard & Mountcastle (24) never observed hypersexuality in their cats. Another explanation for the discrepancy of results is given by Green *et al.* (105) who believe that inadvertent interference with the blood supply to the anterior hippocampus may produce savage behavior, whereas similar vascular disturbances in the basal ganglia may produce a state of apathy resembling placidity.

Observations in man on the effects upon emotional behavior produced by bilateral amygdaloid lesions were mostly made in assaultive psychotics in whom these lesions were placed in an attempt to curb the patients' aggressiveness. In most cases there was a definite decrease in aggressive behavior (106, 202, 226, 228, 240, 244). Some however showed an initial increase in aggressiveness (220), and still others became emotionally labile. Usually quite docile when left alone, they were nevertheless easily provoked into short-lived anger by minor frustrations (220, 227). This and other aspects of these patients' behavior, such as their manner of speech, their motor restlessness and their abnormal interest for such food items as candies and cake, struck some observers as tantamount to a regression to a childish level of behavior (220, 227, 240). Some authors however failed to observe any obvious change in emotional behavior in patients after bilateral amygdalectomy (67, 68, 253).

The development of hypersexuality was a prominent feature in some experimental series (29, 72, 222–224), whereas in others it was not, or only occasionally, noticed (24, 199, 204, 252) and in still others there was a decrease in sexual impulse (241, 249). Green *et al.* (105) found hypersexuality only when the lesion involved the piriform cortex. Amygdaloid lesions sparing this area did not alter sexual behavior. Hypersexuality follows the placement of bilateral lesions only after a long latent period of several weeks. It leads both in the male and the female to increased copulatory and to abnormal sexual behavior (fig. 9), such as homosexual activities, masturbation and attempts at copulation with animals of other species or outside territory. Preoperative castration prevents development of hypersexuality. Once developed, it will gradually disappear when castration is carried out after amygdalectomy (224). This does not prove, however, that increased sex hormone production is the underlying cause of hypersexuality in amygdalectomized animals. It may merely demonstrate that sex hormones are a necessary prerequisite for the manifestation of sexual behavior. Corroborative evidence in favor of this view is the observation that irritative lesions of the rhinencephalon in man, although producing diminution of libido and potency, are not associated with any signs of hypogonadism (77).

FIG. 9. Hypersexuality produced by bilateral amygdaloid lesions in male cats; attempts at copulation with animals of other species or with other males. Note also that no aggressiveness is displayed towards a dog which is approached as a potential sexual mate just as any other animal. [From Schreiner & Kling (223).]

Bilateral amygdaloid lesions in man produced a clear effect on sexual behavior in only one patient who became exhibitionistic (240), whereas a few others seemed to show only a very slight release of sexual impulse and the majority showed no change at all in sexual behavior (67, 68, 106, 220, 227, 253).

In a female monkey it was noticed that bilateral amygdalectomy also affects maternal behavior, since this animal ceased to care for or defend her offspring after the operation (241, 249).

Different types of changes occurring in general motor behavior after amygdalectomy are described. Fairly often, motor restlessness is noted (29, 204, 220, 223, 236) which may (29, 202, 223, 227, 234, 240, 249, 252) or may not (220, 236) follow upon an initial period of apathy. Logorrhea[7] frequently seen in patients after bilateral amygdalectomy may be related to this motor restlessness (220, 240). In contrast to these observations however are reports that in rats bilateral amygdalectomy is followed by a permanent decrease in spontaneous activity (10).

A special form of increased motor activity is that which Klüver & Bucy (143–145) described as 'hyper-

[7] Vocalization was increased in cats (223) but decreased in monkeys (143–145) after bilateral amygdaloid lesions.

metamorphosis.' This is a strong urge to attend and to react to every visual stimulus. Some observers also noted this change after more restricted lesions involving mainly the amygdala (29, 220, 223). Others failed to see it (199, 249).

Strong oral tendencies, an urge to examine all objects by mouth, whether edible, inedible, dangerous or even disgusting, is another prominent behavioral change seen in Klüver & Bucy's monkeys (143–145) and is also reported by many investigators to occur after more restricted lesions involving principally the amygdala (17, 29, 202, 204, 216, 220, 222, 223, 234, 252). Others however did not observe this change (199, 240). This 'oral compulsive behavior' may be closely related to two other components of the Klüver-Bucy syndrome: first, visual agnosia which may represent a compensating mechanism aimed at object discrimination by taste, smell and touch; and second, disturbances in feeding behavior manifested by a compulsive urge to ingest anything indiscriminately (216). One may object to this interpretation on the ground that usually inedible objects are discarded after oral examination. This is however not always the case and may in any event not be very relevant an objection since meat, which a normal monkey would not 'consider' edible, is accepted as food by bilaterally amygdalectomized monkeys (204, 252). The actual amount of food intake is described as normal by some authors (10, 18, 220, 254) and as increased by others (204, 217, 240).

Visual agnosia is the only symptom of the Klüver-Bucy syndrome which most probably is not critically dependent on an amygdaloid lesion as shown by Pribram and his associates (183, 204, 252). However, Sawa and co-workers (220) mention its occurrence after bilateral amygdaloid lesions in man.

The changes produced by bilateral amygdaloid lesions are not static. They evolve in time. Immediately after operation there is often a sleep-like or cataleptic state with apathy and refusal to eat (10, 16, 17, 29, 199, 202, 223, 227, 234, 240, 249, 252). However hyperactive and overaggressive behavior immediately after operation was observed by some other investigators (220, 236). After several days the post-operative apathy clears up and the profound changes in emotional behavior become apparent. Hypersexuality develops only after several weeks or even months (145, 223). Over months or years the behavioral alterations tend to recede slowly. In monkeys hypersexuality and meat-eating are the first to disappear (141), whereas the changes in emotional behavior and hypermetamorphosis are the most resistent (141, 240, 249) and may still be present after many years (141).

The changes produced by bilateral amygdalectomy may be partly at least the consequence of some release of the activity of the ventromedial hypothalamic nucleus since its bilateral destruction in amygdalectomized animals restores aggressiveness and abolishes hypersexuality, oral compulsive behavior and hypermetamorphosis (222, 223). This would indicate that the pathways from the amygdala to this nucleus, demonstrated with anatomical (3) and electrographic (96) methods, mediate an inhibitory influence.

PATHOPHYSIOLOGY

Epilepsy

Revealing insights into the functions of the amygdala can be gained from studies of epileptic seizures originating in this area. It was Hughlings Jackson (123–126) who first recognized late in the last century[8] that seizure discharge originating from this area produces what today is called psychomotor epilepsy (74, 78, 94, 95) or temporal lobe epilepsy with ictal automatism (61, 86, 197, 198). Recent work has clearly demonstrated the correctness of Hughlings Jackson's views (58, 61, 71, 74, 75, 78, 83, 92, 127–129, 134, 176, 179, 181, 198).

The most characteristic feature of the automatic state, so typical of these attacks, is the patient's "loss of capacity to make durable memory records" [Penfield (198); (see also 159)]. This is usually associated with unresponsiveness and a variable degree of loss of understanding, which one may call confusion, while motor control and reception of sensory stimuli is preserved. Thus the patient may be able to indulge in self-inspection or carry out elaborate acts and even avoid obstacles when moving around. If he talks at all, his speech is usually irrelevant to the situation. When interfered with, he often becomes aggressive. Masticatory movements, respiratory and autonomic changes are commonly observed during such an attack. The seizure usually starts with sudden staring, less often with tonic adversive movements, and is often ushered in by an epigastric, cephalic, somatic, gustatory or olfactory sensation, a feeling of fear, and awareness of confusion of thinking or a 'psychical' illusion (40, 61, 75, 84, 86, 174, 176, 197, 198). More rarely observed ictal symptoms are outbursts of rage

[8] Even older descriptions of seizures originating in this area were given by Sander in 1874 (219), Hamilton in 1882 (110) and Anderson in 1887 (19).

with amnesia (79), ictal depressive feelings (251), a feeling of joy (237), sexual excitement (25, 34, 77) or an acute feeling of hunger (76). In patients undergoing surgery for their seizures these ictal symptoms can be reproduced by stimulation of the amygdala (61, 129, 198).

Patients suffering from this type of seizure often present an interictal syndrome which more often involves abnormal behavior than that seen in patients suffering from other forms of epilepsy (91, 213). Gastaut and his collaborators (79) state that 72 per cent of psychomotor epileptics show personality traits which were once regarded to be characteristic for epileptics in general and were therefore described as 'epileptoid constitution' (see also 71, 75, 78, 85, 230, 231). These patients show a striking slowness of movements and thinking and a tendency to perseveration, a demeanor which has been called 'adhesiveness' or 'viscosity' and which contrasts rather strikingly with the propensity of these patients to be provoked into explosive and violent anger, often for causes of the most trifling nature (see also 248). Many psychomotor epileptics also suffer from loss of libido, sexual impotence or frigidity (75, 77) and some show disturbances of their appetite (76, 84). It seems that this complex syndrome is essentially the opposite of that produced by bilateral amygdaloid lesions in animals.[9] A continuous state of subictal irritation by the focus seems to be its cause.[10]

Interictal disturbances can also be demonstrated in monkeys with chronic epileptogenic lesions of the amygdala. Such lesions seriously hamper the establishment of conditioned reactions to any modality of sensory stimuli (185). The fact that this deficit is cured after excision of the epileptogenic focus proves that it is caused by abnormal discharges and not by destruction of nervous tissue.

In animals 'amygdaloid epilepsy' can be produced by injection of alumina cream into the amygdaloid region (81, 83, 89, 185, 186, 190, 212, 232). The seizure pattern in these animals faithfully duplicates the responses obtained by amygdaloid stimulation in unanesthetized animals (fig. 10).

[9] However, symptoms reminiscent of those seen in animals with bilateral amygdaloid lesions are actually seen in a minority of patients indicating loss of function of the temporal rhinencephalic structures either due to bilateral destructive lesions or functional paralysis by excessive firing (79, 161).

[10] Even more suggestive evidence for such continuous irritation is the phenomenon which has been called 'continuous' aura, e.g. in the form of a constant feeling of fear or anxiety in a patient having seizures starting with an aura of fear (225, see also 84).

Sporadic epileptogenic potentials in patients and animals with amygdaloid epileptogenic lesions are recorded over the anterior temporal, insular and uncohippocampal regions (61, 71, 74, 75, 78, 81, 83, 89, 92, 94, 117, 127, 128, 171, 176, 186, 197, 212). Animals with unilateral amygdaloid alumina cream lesions develop after some time a mirror focus in the contralateral amygdala, which finally fires quite independently of the primary lesion (212). Such bilateral foci are frequent findings in human temporal lobe epilepsy (74, 83, 198) and some of them may also originate in this same manner.

Amygdaloid seizures in man and animals often start with an initial 'suppression' of cortical electrical activity which even affects the previously present interictal spike discharges (60, 61, 74, 75, 81, 83, 89, 100, 117, 128, 134, 176, 198, 212). This corticographic response is very similar to the diffuse low-voltage fast pattern which can be produced by amygdaloid stimulation (see p. 1403).

FIG. 10. Different stages of a spontaneous seizure in the cat due to an epileptogenic alumina cream lesion in the left amygdaloid area. The seizure starts with an attention response and slight contraversive turning of the head to the right. Then the pupils dilate and the cat looks frightened; the contralateral forepaw is slightly raised and there is tonic extension with stiffening of the contralateral hind leg. The cat thus assumes a posture as if terrified and about to escape. This is followed by ipsilateral clonic face movements (*top right*) and jaw movements with salivation (*bottom right*). A similar sequence of events is also seen in response to electrical stimulation of the amygdala. [From Naquet (190).]

The study of propagation of amygdaloid seizure activity in animals by the use of the after-discharge method shows a widespread subcortical conduction of such seizures. Thus the basal ganglia, the septal nuclei, the hypothalamus, the subthalamus, the thalamus and the mesencephalon are invaded by the seizure discharge (20, 44, 100, 175). Quite in contrast to this is the limited cortical propagation which is usually restricted to the anterior temporal, insular and uncohippocampal cortex (20, 44, 80, 100, 175). Widespread subcortical conduction may even occur without any neocortical involvement at all (20, 100, 175). Thus it may be explained why the performance of elaborate automatic activities is still possible during ictal automatism since the neocortex is not, or only slightly, invaded by the seizure discharge, while memory recording and consciousness are interfered with due to conduction of seizure discharge into central integrating structures of the higher brain stem and diencephalon (20, 100, 175, 197). The contrast between the extent of subcortical and cortical involvement may be related to the fact that recruitment is a common feature of subcortical and rhinencephalic responses to repetitive amygdaloid stimulation, whereas no such recruitment is seen in the neocortex (97) (see p. 1402). However repetitive amygdaloid stimulation usually does not lead to any appreciable thalamic involvement. It is a reasonable assumption that this may occur under the influence of maximal or nearly maximal repetitive amygdaloid firing as in a seizure discharge.

The preferential pathways of propagation of amygdaloid seizure discharges are to subcortical structures (fig. 11), mainly to the hypothalamus, subthalamus and mesencephalic tegmentum. Increasingly labile is the propagation to the thalamus, temporal cortex and the contralateral temporal lobe including the contralateral amygdala (20, 100). Different results however are reported by Creutzfeldt (44) who found preferential spread to the homolateral anterior and basal cortex, and by Faeth *et al.* (57) who describe a preferential route of propagation to the opposite amygdala and hippocampus and to the ipsilateral temporal cortex. Faeth *et al.* however stimulated the 'amygdala-hippocampal complex' and this may well explain their different results.

Hallucinations

Freeman & Williams (67, 68, 253) advanced the theory that the amygdala plays an important role in the emission and regulation of 'sonar' in chiroptera

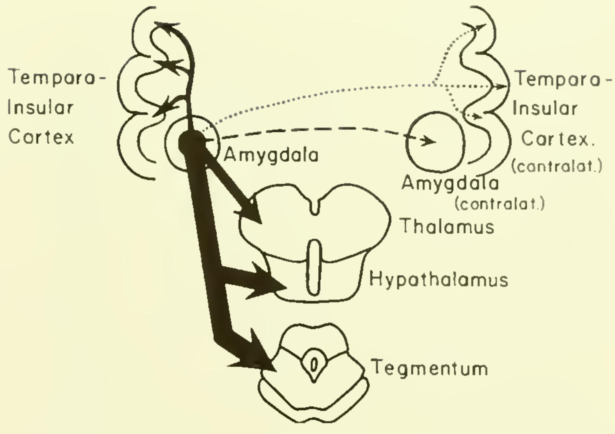

FIG. 11. Preferential pathways of spread of amygdaloid seizure discharges as based on experimental studies in the cat. Note that the most prominent conduction is that into the hypothalamus and mesencephalic tegmentum. [From Gloor (100).]

and cetacea. They believed that auditory hallucinations in man may be related to disturbances in the human counterpart of this 'sonar' apparatus. On this theoretical basis they attempted to cure auditory hallucinations with bilateral excision of the amygdala. There is however not much factual foundation for their hypothesis and it is therefore hardly surprising that no significant number of cures were obtained by this operative procedure.

FUNCTIONAL SIGNIFICANCE OF AMYGDALA

A comparison of physiological studies carried out on the amygdala with those performed on other parts of the rhinencephalon reveals a surprising similarity of function between various parts of this system (99). This similarity is especially close within what Pribram & Kruger (205) have called the 'second system' of the rhinencephalon which comprises the amygdala, the piriform lobe, the orbitofrontal cortex and the septum. It is not legitimate therefore to divorce the discussion of the functional significance of the amygdaloid complex from that of this anatomically more extensive functional system.

A fruitful approach to the understanding of the functional role of this system is to set the results of bilateral lesions against the background of the surprisingly wide spectrum of autonomic and somatomotor functions influenced by rhinencephalic stimulation (99). It then becomes at once apparent that

bilateral amygdaloid or other rhinencephalic lesions fail to produce deficits of the very autonomic and somatomotor functions which are so clearly influenced by rhinencephalic stimulation. The rhinencephalon cannot therefore be essential for their integration. Most of these functions are known to be integrated in the hypothalamus and brain stem. Despite the great similarity of rhinencephalic stimulation responses to those obtained from stimulations of the hypothalamus and brain stem, a great difference in functional significance is thus revealed between the rhinencephalon and those subcortical areas. This noninvolvement of the rhinencephalon in the integration of basic autonomic and somatomotor mechanisms makes it easier to accept the absence of a mosaic of topographical representation of function in this system. It also makes more acceptable the potentially dual character of many rhinencephalic stimulation responses with opposite effects upon the same function apt to occur from the same locus of stimulation.

This unessential character of rhinencephalic function for the integration of basic autonomic and somatomotor mechanisms stresses the importance of the behavioral and mental alterations produced by rhinencephalic stimulations, epileptic discharges and lesions. However here again the situation is not clear-cut and simple. In animals, electrical stimulation brings forth not only reactions of fear and anger but also behavioral patterns of an opposite character, suggesting that a 'rewarding' experience can be elicited by stimulation. Furthermore bilateral lesions have produced placidity as well as its opposite—savage, angry behavior. From the study of the experimental records it seems unlikely that differences in the anatomical location of the site of stimulation or of the lesion could adequately account for these opposite effects.

All these findings suggest a great lability of rhinencephalic function based upon flexible neuronal mechanisms, as revealed by electrographic studies of the amygdaloid projections system (97). It has therefore been suggested that the amygdala and other parts of the rhinencephalon modulate activities integrated in subcortical structures (97, 99, 101).

This modulatory influence is probably of great importance in the organization of complex behavioral mechanisms. Olds (192, 194) advanced the theory that the amygdala and other rhinencephalic structures of the 'second system' may be essential for the elaboration of the reinforcing effect of 'reward' upon instrumental behavior. In view of the clear evidence that other than rewarding experiences, e.g. fear and rage, can be produced by amygdaloid stimulation it seems necessary to broaden this hypothesis in order to include motivational forces other than reward. One may thus conceive of this system as more generally concerned with motivational reinforcement of behavioral patterns. The behavioral alterations produced by amygdaloid lesions support such a view. The basic defect produced by these lesions could then be described as a disturbance in those motivational mechanisms which normally allow the selection of behavior appropriate to a given situation (192, 252). Disturbances in these mechanisms would then account for the indiscriminate fearless approach to any object, animal or person, the indiscriminate reaction to any environmental stimulus described as hypermetamorphosis, the indiscriminate tendency to ingest food and nonfood objects, and the indiscriminate attempts to derive sexual satisfaction from any potential source of gratification. The behavioral disturbances displayed by many psychomotor epileptics give further support to this concept. Constant irritation of this system by an epileptogenic focus seems to produce a tendency for insufficiently motivated outbursts of rage as if the rage responses were triggered by a normally 'subthreshold' motivational stimulus. This broadened concept would also be in accord with the more traditional theories ascribing to the rhinencephalon the role of integrating emotional experience and expression (70, 72, 73, 138, 167–170, 195). The involvement of this system in 'motivational selection' of behavioral patterns would render more meaningful the close anatomical and functional relationship of the amygdala with the hippocampus (96–98), the important role of which in memory recording becomes more and more apparent (182, 228), for it seems evident that the reinforcing effect of such motivational forces as emotion, as well as the laying down of memory traces, are equally essential for the selection of behavioral patterns (194). A close functional association between the nervous substrata subserving these two functions seems therefore to be a necessary prerequisite for their correct interplay.

The functional concept here developed presupposes that the structures supporting these functions show a great flexibility of action and a broad spectrum of influence upon neuronal mechanisms integrating somatomotor and autonomic functions. The experimental data accumulated over the past years clearly show that the amygdaloid complex and other parts of the rhinencephalon would meet these requirements.

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